DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville, MD 20852

Division of Clinical Trial Design and Analysis

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Memorandum

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From: Ilan Irony, M.D., OTRR, DCTDA

Subject: Medical Officer Review

Through: Dwaine Rieves, M.D., Team Leader

Marc K. Walton, M.D., Ph.D., Acting Deputy Director, DCTDA

To: File STN 125058/0

BLA STN 125058/0

Original Submission

BioMarin Pharmaceuticals, Incorporated

ALDURAZYME™

Laronidase

For the Treatment of Mucopolysaccharidosis I

Clinical Review

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Introduction

This document is the medical officer's review of the clinical data submitted with the Biologics License Application (BLA) Submission Tracking Number 125058. This application is for Laronidase (ALDURAZYME), a recombinant enzyme product which is proposed for usage as enzyme replacement therapy for patients with Mucopolysaccharidosis I.

Proposed indication and dose

BioMarin proposes that laronidase is indicated as long term enzyme replacement therapy in patients with Mucopolysaccharidosis I (MPS I, α - L – iduronidase deficiency) to treat the non- central nervous system manifestations of the disease. The proposed dosage regimen of Laronidase is 100 U / kg (0.58 mg / kg) of actual body weight administered once weekly as an intravenous infusion.

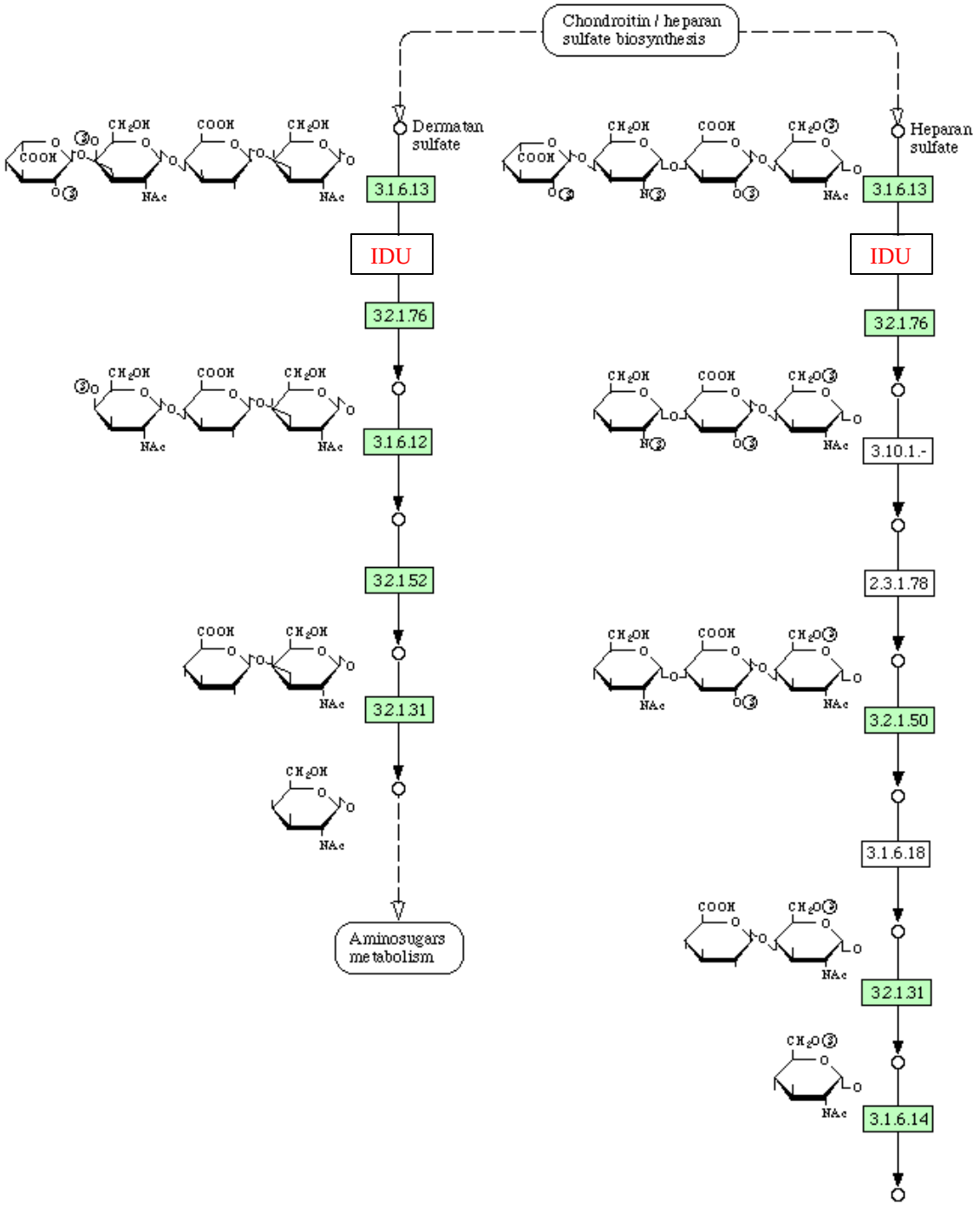
Reviewer's comment: This disorder, as for all forms of lysosomal storage diseases, has complex and multiple organ and tissue manifestations. Despite the variable phenotypes and a broad spectrum of severity, evidence-based determination of a treatment effect on specific endpoints would be required to support a claim of benefit for these endpoints, rather than a claim of general benefit in the management of the disease as a whole.

Biochemical and Clinical Background

Lysosomal storage disorders result from a genetic defect that causes deficient production or function of one or more of the lysosomal enzymes. The enzymatic deficiency results in an abnormal accumulation of metabolites within a lysosome and ultimately disruption of the normal cell function and cell death. Lysosomal storage disorders are usually classified according to the nature of the macromolecule that is abnormally catabolized and consequently accumulates within the lysosome. Sphyngolipidoses (including gangliosidoses) are associated with the accumulation of complex lipids, the basic structure of which is a sphingosine, a long chain amino-alcohol. Oligosaccharidoses or mucolipidoses are associated with the storage of complex glycoproteins. Mucopolysaccharidosis are caused by deficiencies of enzymes needed to degrade glycosaminoglycans (also known as mucopolysaccharides). Glycosaminoglycans themselves are lysosomal degradation products derived by proteolytic removal of the protein core of proteoglycans (macromolecules occurring in the cell membrane and extracellular matrix). Mucopolysaccharidosis I is the subject of this license application, and will be described here briefly.

Mucopolysaccharidosis I (MPS I) is characterized biochemically by the deficiency of the lysosomal enzyme α-L-iduronidase (IDU). This enzyme cleaves the terminal iduronic acid residues of dermatan sulfate and heparan sulfate (Figure 1).

Figure 1. Catabolism of glycosaminoglycans highlighting role of IDU



Source: www.genome.ad.jp/dbget-bin/get_pathway?org_name=hsa&mapno=00531 assessed on October 16, 2002

Experiments in cultured fibroblasts show that the enzyme is made in a precursor form, cleaved intracellularly to a 628 amino acid protein and incorporated with mannose 6-phosphate markers for targeting to lysosomes. The gene encoding IDU is located in the short arm of chromosome 4 (locus 4p16.3) and MPS I is inherited with autosomal recessive transmission. Homozygosity or compound heterozygosity for the W402X (stop codon) and Q70X mutations are the common causes of MPS I with a severe form in affected Caucasian individuals.

Japanese patients with MPS-I have other predominant IDU gene mutations. Historically, MPS I patients have been broadly categorized into three clinical syndromes: Hurler, Hurler-Scheie, and Scheie, representing severe, intermediate, and mild clinical phenotypes, respectively. These classifications are arbitrary categorizations of points on a continuous spectrum of patient phenotypes. Biochemically, patients with the milder disease form retain trace residual amounts of IDU that are sufficient to ameliorate the phenotype to varying degrees. However there is considerable heterogeneity in the severity and symptoms within each phenotype and substantial overlap of the three syndromes. The true incidence of MPS I is unknown, with estimates in the range of 1/76,000 for MPSIH, 1/280,000 for MPS IH-S, and less than 1 in 840,000 live births for MPS IS in Northern Ireland. Semi quantitative analysis of spot urinary glycosaminoglycans can be used for screening, but is subject to both false negative and false positive results. Definitive diagnosis is established by lysosomal enzymes assays in leukocytes, cultured skin fibroblasts or serum. Pre-natal diagnosis is established by IDU assays in cultured cells from amniotic fluid or chorionic villus biopsies. Carrier testing is currently performed with analysis of enzyme activity in family members, but may be superseded by molecular analysis of specific family mutations in the enzyme gene.

Hurler syndrome (MPS IH) is a progressive disorder that affects multiple organs and tissues and leads to death during childhood. The symptoms of MPS IH present between 6 months and 2 years of age. They include inguinal or umbilical hernias, hepatosplenomegaly, coarse facies, deafness, recurrent ear and sinus infections, macroglossia, noisy breathing, obstructive airway disease and sleep apnea, communicating hydrocephalus with increased intracranial pressure, prominent forehead, developmental delay, skeletal deformities (dysostosis multiplex), corneal clouding, joint stiffness, acute cardiomyopathy associated with endocardial fibroelastosis, valvular heart disease and pulmonary hypertension. The most frequent causes of death are related to obstructive airway disease, respiratory infections and cardiac complications.

Symptoms of Hurler-Scheie Syndrome (MPS IH-S) include dysostosis multiplex, corneal clouding, joint stiffness, short stature, deafness, and obstructive airway disease with little or no intellectual dysfunction. The onset of these symptoms is observed between ages 3 and 8 years of age, and death usually occurs in the second or third decade of life, usually from the same complications described in the Hurler patients.

Patients with Scheie Syndrome (MPS IS) have variable amounts of joint stiffness, aortic valve disease, mild hepatosplenomegaly, and corneal clouding, usually without neurologic involvement. Symptoms start in children older than 5 years and the diagnosis is usually

made between 10 and 20 years of age. Patients achieve normal stature and normal lifespan.

Current management of patients with MPS I is restricted to supportive care and treatment of specific complications. Ventriculoperitoneal shunting in moderate to severe hydrocephalus, ventilating tubes and hearing aids, range of motion exercises, tracheostomy and high pressure nasal continuous positive airway pressure, mitral or aortic valve replacement can improve symptoms.

A treatment that can replace the defective enzyme by supplying either cells capable of normal IDU secretion or functional IDU can potentially improve the clinical manifestations of MPS I. Cell culture and animal model experiments have demonstrated feasibility and raised optimism. Despite numerous trials using different enzyme sources, the only significant advance has been transplantation of allogeneic bone marrow in patients with MPS IH, particularly if instituted before the age of 2 years. With stable bone marrow engraftment the biochemical and somatic features revert, and long-term survival is possible. Neuropsychological function and some skeletal abnormalities are not reversed in patients that undergo bone marrow transplantation after age 2. However, limitations in the appropriate donor pool, and the high risks of significant morbidity and mortality make this therapeutic option restricted to a few affected individuals.

With the cloning of complementary DNA for IDU, large scale production of the recombinant human α - L – IDU became possible, with the mannose 6 phosphate sites necessary for targeting lysosomes.

Product Background

Recombinant human α-L-iduronidase (rhIDU) is a 628 amino acid lysosomal hydrolase. The enzyme is a single polypeptide chain of molecular mass 70.1 kilodaltons (from translated cDNA sequence). rhIDU contains six asparagine-linked glycosylation sites, two of which carry the bis mannose-6-phosphate oligomannose7 7 oligosaccharide that binds the target cell surface receptor. The apparent molecular mass of full-length rhIDU by ---------- is approximately 83 kilodaltons, suggesting that posttranslational modifications of rhIDU contribute approximately 13 kilodaltons to the molecular mass.

rhIDU is isolated from cell culture supernatant following growth of a Chinese Hamster Ovary (CHO) cell line transfected with a recombinant expression vector containing the cDNA coding region for human α-L-iduronidase (IDU). rhIDU is purified using ----------. Formulation is completed by concentration to a target protein value of 0.58 mg/mL followed by the addition of polysorbate 80 (10 µg / mL). Laronidase, the drug product, is a liquid solution that is to be diluted for intravenous administration.

The product used in the pre-clinical studies and the Phase 1 / 2 clinical study was originally defined with an activity of 125,000 U/mL and a protein concentration of 0.5 mg/mL. These characteristics of laronidase were subsequently redefined as 100 U /mL activity and 0.58 mg/mL protein concentration in the final 5.3 mL vialing volume. These redefinitions do not

constitute any changes in actual enzyme activity or concentration, rather reflecting changes in assay methodology.

Regulatory History

Development of laronidase was conducted under IND 7334. The original submission of September 19, 1997, contained the protocol for a Phase 1 / 2 clinical study. Subsequently, a single Phase 3 study was conducted.

Pre-clinical studies

Reviewer's comment: It is important to note that the assay for α-L–iduronidase activity was changed during the drug development to make it more reproducible and robust accompanied by a change in the definition of activity unit to be more conventional. As an example the dose used in the Phase 1 / 2 clinical study was reported as 125,000 U, which was determined to be equivalent to 100 U under the revised activity definition. The method for determination of protein concentration was also changed, from ----------, resulting in a small increase, such that the dose of rhIDU that measured 0.5 mg /ml in the ----------assay measured 0.58 mg / ml in the new ---------- assay.

Dosing in all the pharmacodynamic studies was reported on an enzymatic activity basis (U / kg) using the old unit and the ---------- assay. Dosing in the toxicity studies was reported only on a weight basis using the ---------- assay. Most of the pre-clinical study reports present the dose used in a mg / kg basis, except for the pharmacodynamic studies, which also present data in the original activity units for comparison to the published literature.

Toxicology studies

Placebo and dose-controlled acute toxicity studies using single doses of laronidase were conducted in rats and dogs with a dose range of 0.29 to 5.8 mg kg in rats and 0.116 to 11.6 mg/kg in dogs. No treatment related toxicities were found, although dogs had low incidence of emesis and mucoid liquid stools following treatment with laronidase, unrelated to dose. Female rats developed small foci of hepatocellular necrosis of unclear relationship to the treatment and unclear significance.

An intravenous laronidase study in cynomolgus monkeys showed a slight increase in lymphocytes and eosinophils when the highest dose (16.6 mg/kg) was infused weekly for 26 weeks.

Pharmacodynamic studies

In vitro studies were carried out to explore the uptake of laronidase by MPS I patient fibroblasts, its effect on GAG storage and its cell half-life. These studies demonstrated effective laronidase endocytosis by the fibroblasts via a mannose-6-phosphate dependent receptor with a half-maximal uptake at approximately 0.7 nM enzyme. Laronidase reduced GAG storage in MPS I patient fibroblasts with half-maximal reduction at approximately 0.7 pM. The half-life of the enzyme in the fibroblasts was estimated at 5 days.

Reviewer's comment: The sponsor claims this result supports a once weekly dosing regimen, but no in-vivo studies were performed to examine the tissue half-life of the enzyme.

A canine model of MPS I has many features of the human disorder and carries a mutation in the donor splice site of I A 1 of the IDU gene. This mutation results in the null expression of the enzyme.

Studies ranging from 12 days (alternate day intravenous infusion) to 3 months (weekly intravenous infusion) duration demonstrated clearance of GAG lysosomal storage with increase tissue levels of the enzyme in the MPS I dog.

Laronidase was then given to another dog for 13 months also at 25,000 U / kg weekly, and by 6 months progressive improvement was noted with weight gain, greater activity, less corneal clouding, less joint stiffness, and greater mobility, associated with decreased tissue GAG levels. Tissue levels of GAG were still higher than in normal dogs.

Reviewer's comment: This experiment shows that a longer treatment period is required for clinical improvement to become apparent. BioMarin notes that enzyme activity was observed in the brain but no reduction in GAG levels was noted, and speculates that this could be due to the enzyme uptake by the brain capillary endothelial cell, with inability to cross the blood-brain barrier. This reviewer notes that the dose administered to dogs may have been insufficient to saturate the endothelial uptake and testing with higher doses or with intra-thecal administration might have elucidated this hypothesis.

Subsequent studies in the canine model using laronidase at 125,000 versus 500,000 U/kg/week (0.5 or 2.0 mg/kg/week) showed superiority of 9-hour weekly infusions over continuous infusions in raising tissue enzyme levels and decreasing tissue GAG accumulation. More importantly, this study also demonstrated that at the 2.0 mg/kg/week dose, the 9-hour infusion was more effective than continuous infusion at lowering GAG levels in cornea, kidney cortex, liver, myocardium, pancreas, synovium, cerebral cortex, and medulla. There were no significant differences in GAG accumulation within denser connective tissues (i.e. ligaments, cartilage, cornea, atrioventricular valve leaflets).

Reviewer's comment: The sponsor has provided studies with a good animal model of the human disease. However, the studies performed involved very few dogs per experiment, which could not account for the inter-individual variability of responses. The major problem with these pharmacodynamic studies has been that the dose range explored was very narrow, and despite absence of dose-limiting toxicities, BioMarin has not engaged in testing higher doses that could have demonstrated efficacy in tissues that

clearly impact morbidity and mortality in dogs and humans, such as cartilage (tracheal and joints), brain and heart valves. Even within the narrow dose range tested, BioMarin elected to pursue clinical studies with a single dose of 0.58 mg / kg or 100 U / kg (noted in these pre-clinical studies as 125,000 activity units per kg or 0.5 mg / kg) despite evidence that 2 mg /kg (4 times the dose used in clinical trials, on a mg/kg basis) administered in a weekly bolus regimen was superior in the MPS I dog studies.

Safety

Infusion related anaphylactoid reactions were observed in dogs and cats and managed by stopping the infusion, intravenous fluid administration and, if necessary, oxygen supplementation. The most likely cause of these reactions is IgG-mediated complement activation. Anti-histamines treatment prior to the infusions was effective in eliminating or decreasing these reactions. Lowering the infusion rate and the addition of canine serum albumin also mitigated these reactions in long term laronidase administration. BioMarin notes that the clinical grade product is more pure than the one used in the pre-clinical studies, and polysorbate 80 added as a detergent in the clinical grade product can potentially decrease microaggregation. Anaphylactoid reactions were not seen in monkeys or dogs treated with the clinical grade product, even without pre-treatment with antihistamines.

Overview of Clinical Studies

This application contains data from a total of 59 patients with various forms of MPS I. The initial open label study of laronidase has been extended as a single arm, uncontrolled trial. Study ALID-003 enrolled 45 subjects into the single randomized, placebo controlled, double blind trial reported with this application. At the end of the study all subjects were offered participation in an open label single arm laronidase protocol. Subjects previously randomized to placebo were converted to laronidase treatment.

There is also a small ongoing Open Label Study that provides treatment for patients with late-stage MPS I who are seriously ill and do not meet the selection criteria for participation in ongoing clinical studies. As of 29 April 2002, 4 patients had received laronidase treatment in this program.

The sponsor has conducted 3 clinical studies during the clinical development of laronidase (Table 1)

Table 1. Clinical Studies Included in this Submission

Protocol	Study Design	Completion Status / Study Dates	Location/ Number of Centers	Duration of treatment (weeks)	n
ALID-003	Phase 3 Double Blind, Placebo Controlled Randomized	Completed 12/28/00 to 9/6/01	USA:2 Canada: 1 UK: 1 Germany: 1	26	45
ALID-006	Phase 3 Open Label , non-randomized Extension	Ongoing	USA: 13 Canada: 2 UK: 1 Germany: 2	36	45
BIO7500	Phase 1 / 2 Open Label, non-randomized	Ongoing Started 11/28/97	USA: 13	171 (safety)	10
Special Access & ALID-007	Uncontrolled Administration	Ongoing	Australia: 3	35	3
	Single Patient	Completed (subject died)	USA: 1	28	1

A multicenter observational study (ALID-004) was also conducted between 3/1/00 and 5/29/00, to collect normative data in patients with MPS I. The single session survey included 5 centers in the USA and Europe and enrolled 45 patients. The objective was to determine median values for the six minute walk distance test (6MWD) and the forced vital capacity (FVC) in patients with MPS I intended to participate in the Phase 3 clinical trial of laronidase replacement. Those variables were to be used as primary efficacy endpoints for the planned Phase 3 trial.

Reviewer's comment: It is important to note that in the process of discussion of the Phase 3 study design, the sponsor was inclined to investigate the effect on the FVC alone to demonstrate the product efficacy. However FDA asked that the demonstration of efficacy include endpoints of interpretable clinical meaning, since MPS I is a complex disorder with significant morbidity and mortality that extends beyond the pulmonary impairment and small changes in FVC may be of uncertain clinical significance.

45 subjects were enrolled into the study. Of these, 42 subjects could perform reproducible FVC maneuvers. 20 subjects (48%) were male and 22 (52%) were female. 90% of the study population was Caucasian. The mean (± SD) age of the subjects was 16.6 (± 11.2) years. The mean time since first symptoms was 13.0 years (± 10.6) and the mean time since diagnosis was 8.3 years (± 7.0). The mean enzyme activity expressed as a percentage of the lower normal range was 2.1 (± 2.9). The median percentage of predicted normal FVC value (based upon sitting height) was 80.9% (mean 86.9, SD 25.64, range 39.75-151.95). The median percentage of predicted normal FVC value (based upon standing height in the 36 patients for whom this information was available at the time of database lock) was 68.5% (mean 71.0, SD 21.62, range 26.78-111.02). The median 6MWD was 376.5 meters (mean 359.3, SD 115.44, range 65-601). The study sponsor concluded from this survey study:

- It is possible to measure standing heights in MPS I patients. This permits use of more current references for normal FVC values for calculating percent of predicted FVC.
- FVC can be performed reproducibly in MPS I patients
- The median values obtained in those patients whose percentage of predicted FVC values were less than 80% can be used to balance the randomization in the Phase III clinical trial.
- The median value for the distance walked in six minutes was high. It would seem unlikely that patients will demonstrate the improvements necessary for a clinically meaningful difference given that they are already walking these large distances in the 6MWD.

Study BIO7500

"Phase 1 / 2, Open-Label Study of Recombinant Human α - L – Iduronidase as Enzyme Replacement Treatment for Mucopolysaccharidosis I (MPS I)".

Overview

This study was conducted under IND 7334 according to Protocol BIO7500-001. The study started on November 28, 1997 and is still being conducted.

While the study is still ongoing, the study report contains safety and clinical outcome data derived from a 152 week period. The original protocol submitted proposed a 26 week study. The study period was amended on September 13, 1998 to extend the trial to 104 weeks and on December 9, 1999 to beyond 104 weeks of continued treatment with laronidase. The product was manufactured at ---------- and BioMarin Pharmaceutical Inc. ---------- for the majority of the study period. A revised production process took place and manufacturing was transferred to BioMarin's Galli Drive ("GD") facility. The GD product was formulated with polysorbate 80, which was thought to decrease microaggregation and reduce the risk of anaphylactoid reactions. A 7 week crossover sub study was performed in seven of the eight subjects enrolled at the time of the production transfer, in order to provide preliminary clinical evidence of comparability of Aldurazyme manufactured by the new GD process to that made by the earlier --- process by assessment of safety profile, pharmacokinetic and pharmacodynamic parameters. The crossover study started between Study Weeks 119 and 130 for different subjects in a staggered fashion. The analyses focused on the results of the plasma enzyme activity level 20 minutes post-infusion and the mean urinary GAG's and several safety endpoints (including immunogenicity) comparing the --- product with the GD product with the Wilcoxon signed-rank test. The results in this report demonstrate that the GD product had a comparable safety profile to the --- product in the seven subjects that participated in the crossover study. An apparent increase in plasma enzyme activity 20 minutes after completion of infusion was observed with GD treatment as compared to --- treatment.

Reviewer's comment: The sponsor also showed data on the mean urinary GAG's levels before and after the crossover that indicates a trend in decrease of this variable that did not reach statistical significance. This data could be interpreted as part of the continued

decreased in GAG levels observed throughout the study, but if coupled with the information in the above paragraph could represent an increase in potency of the product manufactured at the Galli Drive (GD) facility.

Protocol

Title: "Phase 1 / 2, Open-Label Study of Recombinant Human α - L – Iduronidase as Enzyme Replacement Treatment for Mucopolysaccharidosis I (MPS I)". Protocol BIO7500-001. The study was initiated on November 28, 1997 and the reporting period included in the corresponding study report included in this submission ended on March 30, 2001. Six protocol amendments occurred after initiation of the study. These served largely to clarify certain study criteria or procedures, or to extend the study duration, and are incorporated in the following description.

Design

Open label non-randomized, single dose, multicenter, phase 1 study in 10 subjects with MPS I. Effect of laronidase treatment was compared to pre-treatment levels. The study drug was to be administered intravenously on a weekly basis initially for a period of 26 weeks. Subsequent amendments to the protocol extended the study period to 152 weeks.

Reviewer's comment: the sponsor classified this design as "patients serving as their own control" but this is in reality an uncontrolled study.

Reviewer's comment: this study is classified as a multicenter study, but the design is such that all eligible subjects receive the first 6 weeks of product administration at one site (Harbor-UCLA Clinical Research Center) and would have to return to this site for efficacy assessments at 12, 26, 52 and 104 weeks of treatment. This design impairs the analysis of between-sites safety and clinical outcome data (not a study goal).

Objectives

- Assess the safety of repeated infusions of laronidase
- Assess the effect of repeated infusions of laronidase in the reduction of lysosomal storage as assessed by liver and spleen size and urinary GAG excretion and in clinical conditions caused by MPS I, including joint disease, cardiac disease, sleep apnea/airway obstruction, and eye disease

Patients

Inclusion criteria:

- Male and female patients with a clinical and enzymatic diagnosis of MPS I, as confirmed by clinical and enzymatic assessments by the Study Investigators.

- Patients at least 5 years of age.
- Patients with significant physical disease indicative of MPS I, including enlarged liver or spleen size (= 1.5 times normal for age) and elevated urinary GAG (= 5 times normal for age).

Exclusion Criteria:

- Patients who were critically ill. Critical health conditions included congestive heart failure, serious respiratory compromise with chronic hypoxia or pulmonary hypertension, serious spinal cord compression with evidence of substantial neurologic compromise, or any other conditions which could have prevented the child from cooperating and tolerating the experimental protocol or might be expected to lead to death or incapacitation within the study period.
- Patients who had previously undergone bone marrow transplant.
- Patients who received an investigational drug or procedure within 30 days of study enrollment.

Treatment assignment / randomization

In this non-randomized study all eligible subjects enrolled were assigned to active treatment.

Product information and administration

Laronidase was diluted in normal saline with 0.1% (1.0 mg/mL) human serum albumin. The total laronidase dose was 125,000 U/kg (100 U/kg redefined units). The diluted enzyme was infused over a 3-4 hour period with continuous cardiorespiratory and pulse oximetry monitoring. Infusion was started 10 - 30 minutes after intravenous diphenidramine pre-medication. During the first hour, the enzyme was infused at a rate of 50 U/kg/min equivalent to 3,000 U/kg/hr. During the second and third hours, the rest of the dose was administered at a maximum rate of 61,000 U/kg/hr.

Reviewer's comment: The dose and dosing regimen are derived from the pre-clinical studies summarized above. The sponsor has not conducted any exploration of the product related to dose escalation or variations in dosing regimens for optimization of pharmacodynamic variables.

Evaluations

a. Liver and spleen volume were assessed at pre-treatment, and weeks 6, 12, 26, 52, and 104. Outlines of the organs were identified in each of the 1 cm sections obtained by MRI

and integrated to determine volume. Organ weight as a percentage of body weight was determined by assuming the organ density to be 1 g / ml. These evaluations were performed by an unblinded radiologist in real time, and at the end of 52 weeks of study by a radiologist blinded to subject's identity and timepoint of the visit analyzing organ volumes in a randomized fashion. These data were compared to healthy children and adolescents liver and spleen weights in proportion to the average weight for their age. Liver and spleen volume data is reported through week 104 in the unblinded study.

b. Urinary GAG was collected at pre-treatment (3 baseline specimens) and weekly for the first 6 weeks, every 2 weeks to week 26, every 4 weeks to week 52, every 12 weeks to week 100, at week 104, and every 12 weeks until week 152. All determinations were made at Harbor-UCLA by a validated method using Alcyan blue dye and quantification by spectrophotometer. The values were corrected by urine creatinine concentration and expressed as micrograms of GAG per mg of creatinine. The mean urinary GAG levels were calculated for the periods extending from week 16 to 26, 27 to 52, 53 to 104 and 105 to 152.

   Reviewer's comment: These integrated, mean urinary GAG measurements were not prospectively defined in the original protocol or its amendments.

c. Joint range of motion (ROM) of shoulder in flexion and extension, knee in flexion and extension, and elbow in extension. These measurements were obtained by a single physical therapist using a goniometer. 5 independent measurements for each joint and for each visit were obtained and averaged. Joint ROM was assessed at pre-treatment, weeks 6, 12, 26, 52, and 104.

d. Cardiac function was assessed in a prospectively defined but unvalidated "cardiac scoring system" which is a composite score of EKG (weight 3), echocardiogram (weight 5), history (weight 4), physical examination (weight 4), and radiological findings (weight 4). These scores were obtained at pre-treatment and at weeks 12, 26, 52, and 104. At these timepoints, the subject was also assessed according to the New York Heart Association functional classification.

e. Airway obstruction was assessed by a variety of parameters measured during polysomnography to investigate the frequency of apnea (cessation of airflow for 10 or more seconds), hypopnea (50% decrease in airflow per breath accompanied by arousal or desaturation), as well as minutes of hypoxia (oxygen saturation below 90%). Sleep studies were performed at pre-treatment, week 26, and if previously abnormal, at weeks 52 and 104. MRI assessments of the tongue and measurement of the airway index (ratio of mid-sagittal anterior-posterior width of the pharyngeal and tracheal airway to total width of the pharynx) were performed by an unblinded radiologist at pre-treatment and at weeks 6, 12, 26, 52 and 104.

f. Eye disease was assessed by a combination of visual acuity testing, complete ophthalmologic exam, intraocular pressure measurements, corneal photographs at pre-treatment, and at weeks 12, 26, 52, and 104.

g. Central nervous system abnormalities were assessed by brain and cervical cord MRI at pre-treatment, and at weeks 6, 12, 26, 52, and 104, by lumbar puncture if there were no

contraindications for the procedure at pre-treatment and at week 26, and by a pediatric neurologist examination at pre-treatment and weeks 12, 26, 52, and 104. In addition the Wechsler Intelligence Scale was administered at pre-treatment and at week 26. Somatosensory evoked potentials (SEP) were originally scheduled for pretreatment and Weeks 12 and 26 but this assessment was discontinued after pre-treatment due to study-unrelated reasons.

h. Genetic skeletal surveys were performed at pre-treatment and weeks 26, 52, and 104.

i. Height and weight were assessed from health records obtained from the 2 years prior to treatment with rhIDU to establish baseline growth rates, and every 4 weeks to week 52, and every 12 weeks to week 152 during treatment with rhIDU in pre-pubertal subjects (age 5 to 12). Only those assessments performed at Harbor-UCLA were used in the analysis of the results.

j. Safety assessments included any adverse events during the study, measurement of vital signs, pulse oximetry, cardiorespiratory monitoring, EKG, physical examinations, complete blood counts, serum chemistries, and urinalysis. The laboratory assessments were performed weekly for 6 weeks, every 2 weeks to week 26, every 4 weeks to week 52 and every 12 weeks to week 152. 24 hour creatinine clearance was performed at pre-treatment and weeks 12, 26, 52 and 104. Complement testing (CH50, C3 and C4) was done pre- and post-infusion, at pre-treatment and weeks 4, 6, 12, 26, 52, and 104. ELISA assessments for IgG serum antibodies against rhIDU with Western blot specificity confirmation were performed at pre-treatment and weeks 1, every other week to week 26, every 4 weeks to week 52, and every 12 weeks to week 152.

k. Enzyme activity was assessed in buccal brushings at pre-treatment and weekly to week 6, every 2 weeks to week 26, every 4 weeks to week 52 and every 12 weeks to week 104. Enzyme activity was also assessed in leukocytes at pre-treatment and at weeks 2, 6, 12, and 26.

l. Pharmacokinetic studies were performed at pre-treatment, and weeks 1, 2, 12 and 26. Pharmacokinetic studies were also performed on Week 6 for subjects 001 and 002, in addition to the other timepoints.

Safety Monitoring

A study monitor designated by BioMarin would monitor both safety and study conduct at the study sites.

Endpoints

Primary endpoints: The primary endpoints cited in the original protocol were:

1. Proportion of subjects with 20 % reduction of the excess size of either liver or spleen or both. In order to calculate the excess organ size the sponsor proposed to subtract the normal organ size, which in the original protocol was estimated as 2.5 % of body weight for the liver and 0.2 % of body weight for the spleen.

Reviewer's comment: This endpoint has changed substantially in subsequent amendments of the protocol. Amendment 1 of 3/3/98 revised the definition of a significant reduction in organomegaly to a 20 % reduction in the total size of either the liver or the spleen or both. The sponsor justifies the 20 % reduction in organomegaly as a clinical goal based on the published studies of algluceradase in Gaucher as well as the transplantation data in patients with MPS I. However, it is unclear how one can extrapolate the clinical meaning of hepatomegaly in one disorder or with one treatment to a different disorder or different treatment. The timepoint for assessment of this endpoint has been changed since the original study proposed had a 26 week duration, and this was extended in subsequent amendments.

2. % reduction in urinary GAG excretion as calculated by taking the average of the pretreatment samples compared with the average of samples from the last 6 weeks of therapy.

   Reviewer's comment: The definition of endpoint for analysis was very vague in the original protocol. Amendment 2 (9/13/98) revised the definition in the statistical analytical plan as "the four pre-treatment values will be averaged and compared with the last six specimens taken through week 26". As the study duration was extended, the timepoint for endpoint comparison has been modified.

   A general comment related to the analysis of "efficacy" endpoints is that this study is uncontrolled, and variations in these endpoints would demonstrate, at best, bioactivity to guide more definitive studies.

   Secondary endpoints:

1. Cardiac ejection fraction, valvular regurgitation, pulmonary hypertension as assessed by the cardiac scoring system, and NYHA classification
2. Corneal clouding, and visual acuity
3. Joint stiffness / range of motion, based on goniometer, subjective reports of stiffness or pain, as well as video examinations of standard motions.

   Safety endpoints:

   Adverse events, laboratory abnormalities and immunogenicity data throughout the study period.

Statistical analysis

The original protocol submitted does not plan for any comparative statistical analyses. Amendment 1 revises the statistical plan to perform ANOVA on the size reduction of liver and spleen and a 2-tailed Student's t test for comparisons of urinary GAG mean individual variations pre- and post-treatment with laronidase. The protocol proposes the signed rank test as well as repeated measures ANOVA for analyses of some of the secondary endpoints.

Reviewer's comments: In this uncontrolled study, pre- and post-treatment comparisons are not meaningful in support of laronidase efficacy.

Study Conduct

Study Conduct was monitored by 2 contract research organizations (CRO's) during the study period: from 11/28/97 until 6/12/2000 Inveresk Research was charged with study monitoring and from 6/12/00 until the end of the study period Abt Associates Clinical Trials monitored study conduct.

Database Integrity

All completed and reviewed CRFs were delivered to the appropriate CRO's. At each site, the data were entered and validated, with data quality assurance procedures.

This study report includes data collected through March 30, 2001. As of this date, the first patient enrolled had completed Week 171 and the last patient enrolled had completed Week 152. Data listings include all data collected through March 30, 2001. Summary tables include data collected up to and including Week 152. Database lock occurred on September 27, 2001.

Formal Protocol Modifications

This review will highlight only the most significant revisions described in the amendments to this protocol, which are not included in the final protocol described previously.

Amendment 5 (6/12/00) initiated the crossover study for collection of safety, pharmacokinetic and pharmacodynamic data for the revised production process at the GD facility compared to the original process at the --- facility.

Additional analyses of height and weight growth rates were performed for pre-pubertal subjects. For these subjects, the pre- and during-treatment growth rates were calculated as follows: for each subject individually, linear regression was used to obtain separate lines of best fit for the pre- and post-treatment height data versus time point. The pretreatment growth rates were calculated using data up to 2 years prior to treatment (if available). Comparisons of the pre- and post-treatment growth rates were then made using paired t-tests.

Some subjects with missing baseline shoulder flexion or extension data were excluded from the analyses.

Protocol Violations

The most common deviations involved variations from protocol-specified collection times for safety and efficacy assessments, particularly laboratory evaluations (urinalysis, urinalysis with microscopy, CBC, and blood chemistries) and urinary GAG measurements. Most variations resulted from missed study visits. All 10 subjects missed a mean of 19.8 infusions due to frequent unavailability of study drug from December 1998 through December 1999.

Reviewer's comment: The sponsor does not explain the unavailability of laronidase during the study period. The sponsor states that 66% of missed infusions are due to laronidase unavailability, but this figure is inconsistent with the Appendix that lists protocol violations.

FDA site inspection findings

No site inspections have been performed for this study.

Results

Subject disposition

Ten subjects were enrolled into this study. The first subject signed the consent form and was enrolled on November 28, 1997, the first study dose was given on December 19, 1997, and the last subject completed the 152-week timepoint on March 29, 2001. All 10 subjects successfully completed the first 52 weeks of the study, and 8 subjects were active at Week 152. Subject 008 died between Weeks 103 and Week 104 of a viral illness. Subject 002 died 19 days after the patient's last study drug infusion at Week 137 of complications following spinal fusion surgery for worsening of scoliosis.

Baseline characteristics

Table 2 shows the demographic and relevant baseline characteristics of the subjects enrolled in this study.

Table 2. Demographic and baseline characteristics

Subject	Age (yrs)	Height (cm)	Weight (kg)	Gender	Race	Clinical Status
001	17	132.5	38.1	M	White	MPS IH-S
002	10	121	22.6	F	White	MPS IH-S
003	9	122.5	27	M	White	MPS IH-S
004	8	125	34.6	M	White	MPS IH-S
005	12	127	24.4	M	White	MPS IH-S
006	22	152.7	64.5	M	White	MPS IH-S
007	17	160	57.2	F	White	MPS IS
008	5	87	14.8	F	White	MPS IH
009	9	118.5	24.2	F	White	MPS IH-S
010	14	160	54.6	M	White	MPS IH-S

There were 6 pre-pubertal subjects in the study. These subjects covered a broad spectrum of clinical presentation. The Principal Investigator / Medical Monitor used a protocol classification of MPS I phenotypes to describe the subjects disorder severity at the time of enrollment. Under this classification one subject had mild disease (MPS IS, Scheie), 8 subjects had moderate disease (MPS IH-S, Hurler-Scheie) and one subject had severe disease (MPS IH, Hurler). All subjects had in common the wide spectrum of MPS I impairments, with unknown and variable intensity in each affected organ, tissue or functional system. Most of the concomitant medications used by these subjects at the time of entry were analgesics or anti-inflammatory agents for relief of headaches or other pains.

Reviewer's comment: It is important to note that the classification is based on the subjective impression based on the overall degree of organ or tissue impairment seen at a specific age range.

Study drug exposure

Ten subjects participated in this uncontrolled, open label study and have received by the time of the study report weekly intravenous infusions of laronidase for an average 151 weeks (range 103 – 171).
All subjects completed the first 52 weeks of the study, 9 subjects completed 104 weeks, and 8 subjects completed 152 weeks.
The mean (± SD) number of administered infusions per subject was 115.0 (± 17.5, range 82 to 135). As mentioned under Protocol Violations, the majority of missed infusions were due to unavailability of the study drug. Most of the other infusions were missed because of patient illnesses or surgeries, parents' illnesses, logistical problems in getting to the clinic, vacations, or decisions on the part of the subject or parents to receive infusions less

frequently than once a week. Missed infusions were examined by study period— Weeks 1 - 52, Weeks 53 - 104, and Week 105 through 30 March 2001. Study-drug unavailability was more prevalent in study period Weeks 53 -104 for the first subjects enrolled, and study period Weeks 26 - 88 for the last subjects enrolled. The percent of missed infusions due to drug unavailability rose from 22% in Weeks 1 to 52, to 78% in Weeks 53 to 104. No infusions were missed due to drug unavailability from Week 105 to the end of the study period.

Primary endpoints

Hepatomegaly

Results of the blinded review of liver volumes are reported in Table 3. Due to the wide variation in liver volumes at baseline, these results were normalized as percent reduction from baseline for each subject and averaged.

Table 3. Mean normalized liver volume as a percentage of pre-treatment

Time	Mean	SD	# Subjects with = 20 % decrease (n=10)
Pre-treatment	100	0	N/A
Week 6	79.9	6.5	5
Week 12	78.2	6.1	6
Week 26	76.6	10.2	8
Week 52	75.0	9.2	7

These evaluations were performed by an unblinded radiologist in real time. At the end of 52 weeks of this study the liver imaging was read by a radiologist blinded to subject's identity and timepoint of the visit analyzing organ volumes in a randomized fashion.

The unblinded MRI evaluations showed the precision of the mean normalized volumes to be within 3% of the blinded mean readings for all timepoints. The 3 subjects that did not achieve the stated endpoint of 20 % reduction had liver volumes in the normal range for their ages by week 52, and achieved the 20% or greater reduction in liver volume in the unblinded readings at week 104.

Splenomegaly

Results of MRI blinded review of the spleen volumes paralleled those obtained for liver volumes. 7 of the 10 subjects demonstrated a = 20% reduction at week 6. Subject 009 developed clarithromycin-induced hepatitis just prior to the Week 26 imaging timepoint, with a sharp increase in liver and particularly spleen size to twice her baseline volume. As her serum liver enzymes normalized by week 46, both the liver and spleen volumes returned to normal.

In conclusion, using blinded MRI readings, 7 of 10 subjects had a greater than 20% reduction in liver volumes at Week 52, and 5 of the 10 subjects had a 20% reduction in

spleen volume at Weeks 26 and 52. Using unblinded MRI readings, 9 of the 10 subjects had normalized liver size by week 52 (8 / 9 by week 104) and 2 of the ten subjects had normalized spleen volumes by weeks 52 (1 / 9 by week 104).

Biomarin believes (----------) that the reduction in liver and spleen sizes caused improvements in comfort and endurance and the ability to eat and breathe, and implied an important clinical benefit related to this effect.

Reviewer's comment: It is important to note that even though the reduction in liver and spleen volumes was clearly demonstrated, its impact on general well being of the subjects may have been overstated by other factors, including the fact that this is an open label, uncontrolled, unblinded study.

Urinary Glycosaminoglycans

All subjects had elevated urinary GAG levels prior to treatment that were generally proportional to the severity of disease in this limited sample of MPS I subjects. For example, the most severely affected subject (008) had urinary GAG exceeding 500 µg GAG/mg creatinine, whereas the subjects with the mildest disease (003 and 007) had levels of 63.25–112.8 µg GAG/mg creatinine. Table 4 shows the mean normalized urinary GAG level reported as percentage of baseline from pre-treatment to week 152. By week 152 mean GAG levels were within the normal range.

Table 4. Mean normalized urinary GAG as a percentage of pre-treatment

Time	Mean	SD	n	# Subjects with = 50 % decrease (n=10)
Pre-treatment	100	0	10	N/A
Week 6	31.8	5.9	10	10
Week 12	33.6	9.0	10	10
Week 26	31.3	8.2	10	10
Week 52	37.2	11.3	10	8
Week 104	26.4	6.7	9*	9
Week 152	21.5	9.3	7**	7

* Subject 008 died before week 104

** Subject 002 died before week 152

To obtain an overall assessment of the reduction in urinary GAG levels and reduce the variability in levels caused by known physiological variation, mean pretreatment levels were compared with the mean of the urinary GAG determinations made between Weeks 27 and 52, the mean of the determinations made between Weeks 53 and 104, and the mean of the determinations made between Weeks 105 and 152. When the mean urinary GAG level from Weeks 27 to 52 was compared with the pretreatment level for each subject, all 10 subjects met the 50% reduction criterion. The mean pretreatment excretion level was 220.64 µg GAG/mg creatinine and the mean excretion level for Weeks 27-52 was 81.12

µg GAG/mg creatinine, representing a mean reduction of 63%. The mean excretion level for Weeks 53 to 104 was 74.42 µg GAG/mg creatinine, a mean 66% reduction, and the mean excretion level for Weeks 105 to 152 was 41.60 µg GAG/mg creatinine, a mean 81% reduction.

Mean (± SD) urinary GAG in 68 healthy subjects is as follows: 32.4 ± 6.9 µg GAG/ mg creatinine for ages 3 – 12 (n=42), 14.9 ± 3.4 µg GAG/mg creatinine for ages 13-18 (n=12), and 8.5 ± 1.8 µg GAG/mg creatinine for ages 19-52.

Reviewer's comment: This study provides indication of laronidase activity through the substantial but incomplete reduction in urinary GAG levels. The sites of enzyme action and the extent of tissue and organ function recovery cannot be inferred from these data. Similarly, the clinical significance of this finding remains unclear.

Secondary endpoints

Joint ROM

Subjects were evaluated for shoulder flexion and extension, knee flexion and extension, and elbow extension. Results were analyzed for changes in ROM (the angle of a limb relative to the body at maximal flexion or extension) and changes in degrees of restriction of ROM (mean degrees of movement in an age-adjusted normal population minus the degrees of movement in the MPS I subjects).

By Week 26, the majority of subjects showed some improvement in ROM in one or more joints, although inter-subject variability was large. The movements that showed the most improvements at Week 52 were shoulder flexion, knee extension, and elbow extension (Table 5)

The sponsor indicates that the improvements in joint ROM were reflected in patient self-reports of improved hand dexterity and grip, being able to walk more easily, and being able to engage in activities, such as sports, that require arm and shoulder movements.

Table 5. Mean (± SD) Joint ROM and changes from pre-treatment

Joint	Time	Mean ± SD (angle)	Mean (± SD) change from pre-treatment
R Shoulder flexion	**Pre-treatment**	100.6 ± 17.5	28.1 ± 21.5
	Week 52	128.7 ± 16.2	
L Shoulder flexion	**Pre-treatment**	101.2 ± 18.5	26.1 ± 26.8
	Week 52	127.4 ± 17.6	
R Shoulder extension	**Pre-treatment**	32.1 ± 14.0	5.1 ± 19.1
	Week 52	37.2 ± 7.1	
L Shoulder extension	**Pre-treatment**	26.8 ± 6.9	7.6 ± 12.8
	Week 52	34.4 ± 7.5	
R Elbow extension	**Pre-treatment**	156.7 ± 13.4	7.0 ± 6.3
	Week 52	163.7 ± 13.6	
L Elbow extension	**Pre-treatment**	156.1 ± 19.1	7.1 ± 9.0
	Week 52	163.2 ± 16.7	
R Knee flexion	**Pre-treatment**	126.6 ± 14.1	4.7 ± 5.0
	Week 52	131.3 ± 14.4	
L Knee flexion	**Pre-treatment**	126.6 ± 19.7	3.6 ± 8.8
	Week 52	130.1 ± 13.7	
R Knee extension	**Pre-treatment**	172.0 ± 11.0	3.5 ± 10.4
	Week 52	175.5 ± 5.6	
L Knee extension	**Pre-treatment**	171.3 ± 11.0	2.8 ± 6.4
	Week 52	174.1 ± 6.3	

Reviewer's comment: The increase in ROM for some joints was modest, although the mean changes seem to be favorable to the laronidase treatment. Caution should be exercised in the interpretation of this unblinded uncontrolled study in correlating the modest ROM changes to improvements seen in daily activities.

Cardiac Function

The subjects in this study exhibited typical MPS I cardiac disease, including valvular insufficiency, pulmonary hypertension, and congestive heart failure, although only Subject 006 was in serious heart failure at the start of the study.

At Week 26, 3 of 10 subjects had improvements in NYHA scores. After 52 and 104 weeks of treatment, NYHA scores improved in 10 of 10 and 9 of 9 subjects, respectively, with 6 subjects achieving normal scores of Class I. No subject was in Class I at pretreatment.

Outcomes of echocardiographic changes in heart valve function were more heterogeneous among the subjects compared to the more subjective assessment of NYHA scores. Tricuspid regurgitation modestly improved in 6 of 10 subjects at Week 52 and in 6 of 9 subjects at Week 104. Subject 007 had substantial worsening of mitral valve function at Week 52. Subject 006, who entered the study with the most serious cardiac disease, was improved at Week 52, with resolution of pitting edema and dyspnea at rest, decreased left ventricular diameter and the return of sinus rhythm. These changes were sustained at Week 104, except for left ventricular diameter and left atrial enlargement, which increased to pretreatment levels.

Reviewer's comment: The data suggest inconsistent echocardiographic improvement in a few subjects with underlying cardiac disorders in this small uncontrolled study. In contrast the improvement seen using the NYHA scores is more open to the bias inherent in open label studies. These findings are not surprising in view of the lack of effect on GAG accumulation in heart valve and myocardium in the canine model of MPS I described above. Even though the endpoint of cardiac function is very important for morbidity and mortality in this disease, demonstration of significant effects on heart valve dysfunction and thickness, pulmonary pressures and overall cardiac function would require a controlled long term study.

Polysomnography and airway evaluations

Six subjects who had sleep apnea at pre-treatment demonstrated improvement in the number of apnea episodes by week 26. Five of the 9 subjects with pre-treatment hypopneas showed improvement in the number of hypopneas per night by week 26. On the other hand, subjects 008 and 010 had an increase in the number of hypopnea events by week 26. Subjects 002 and 006 had a substantial decrease in the number of minutes with hypoxia (oxygen saturation less than 90%) per night at week 26 (from 48 minutes to 1 minute and from 61 minutes to 28 minutes, respectively). Subject 008 had worsening of sleep apneic and hypopneic episodes, which the sponsor attributed to a decline in pharyngeal tone caused by high pressure hydrocephalus. The apnea hypopnea index (AHI) improved in 7 out of 10 subjects, and the mean AHI decreased from 2.08 to 0.97 (53% reduction) at week 26.

Other measures of airway function (airway index and tongue diameter) showed inconclusive results, in part due to technical difficulties

Eye disease

Three subjects had improvement in visual acuity by week 52, and with additional favorable changes noted at week 104. No changes were observed in intra-ocular pressure or in corneal clouding.

CNS abnormalities

MRI studies of the brain and cervical cord pretreatment demonstrated the substantial pathology expected in MPS I patients. This included perivascular storage, meningeal thickening and spinal cord compression or restriction, and miscellaneous other findings.

In nearly all cases, there were no substantial changes seen on MRI during the 104-week course of laronidase treatment. Pre-treatment cervical MRIs demonstrated narrowing of the cervical canal in all subjects due to lysosomal storage in the meninges and in related bony abnormalities. No substantial changes were observed on MRI through the Week 104 assessment except for one subject (009) who had a first notation of cervical cord compression at Week 104.
Developmental regression was not changed significantly in the single subject with severe disease at pre-treatment (Subject 008) and the Week 26 MRI showed worsening hydrocephalus. CSF GAG levels fell to normal or close to normal in 3 of 4 subjects with abnormally high levels of GAG at pre-treatment (Subject 008 had CSF GAG levels unchanged from pre-treatment to week 26).

Reviewer's comment: These findings are consistent with the lack of enzyme activity in the central nervous system. They are also similar to those pre-clinical studies showing absence of CNS effects in dogs affected by MPS I.

Bone evaluations

No significant changes were observed in the radiologic skeletal surveys performed during the study. All subjects had radiologic evidence of odontoid dysplasia and dysostosis multiplex, commonly seen in patients with MPS I.

Height and weight

In 6 pre-pubertal subjects, height increased by a mean of 6.0 cm or 5.13% (range of 3.1 to 10 cm) at Week 52 and increased by a mean of 10.0 cm or 8.39% (range 4.8 to 16.7 cm) at Week 104. Weight increased by a mean of 4.2 kg or 15.83% (range of 1.2 to 9.6 kg) at Week 52 and increased by a mean of 7.9 kg or 29.72% (range 0.3 to 13.8 kg) at Week 104 in these subjects.

Mean growth rates increased from an estimated 2.80 cm / yr at pre-treatment to 5.32 cm / yr at Week 52 for height and from 1.65 kg / yr to 3.49 kg / yr for weight. Height growth rate normalized for 3 of 6 pre-pubertal subjects at Week 52. Weight growth rate normalized for 2 of the 6 pre-pubertal subjects at Week 52.

Pharmacokinetics

Intravenous administration of laronidase (125,000 U/kg) resulted in significant circulating plasma IDU activity levels of IDU for periods of 3 hours or more.

The circulating levels of IDU achieved peak at 100-200 U/ml for the majority of infusions, which was approximately 10 times the half-maximal uptake of the enzyme in vitro.

The mean circulating half-life (t½) of IDU was approximately 1.8 to 1.9 hours at Weeks 1 and 2 and decreased to 1.2 to 1.4 hours at Weeks 12 and 26 in 7 of the 10 subjects.

Differences in pharmacokinetic parameters did not correspond to differences in urinary GAG excretion.

In examining the question of factors responsible for variations in pharmacokinetic parameters, the sponsor found that presence of antibodies to laronidase did not correlate with a decrease in terminal half-lives by linear regression analysis. The 3 subjects with

consistent IDU-specific antibodies did not have consistent and clear changes—either increased or decreased half-life—compared to patients without IDU-specific antibodies. In addition, no relationship was found between urinary GAG levels, enzyme activity in buccal mucosa brushings and pharmacokinetic parameters.

MPS I phenotype-genotype studies

At baseline, MPS I subjects in this study were deficient in α - L - iduronidase activity and had levels that were 0.003 to 0.25% of those found in cultured fibroblasts from normal individuals.

The level of residual enzyme activity was loosely related to clinical severity: patients with greater residual enzyme activity generally had milder phenotypes. A wide variety of genotypes caused the enzyme deficiency state in these subjects and no subject had a known double null (no enzyme protein producing) mutation.

Enzyme uptake into buccal mucosa and leukocytes

Prior to treatment all subjects had very little or undetectable α - L –iduronidase in their buccal mucosa or peripheral leukocytes.

By the Week 2 pre-infusion assessment, enzyme was detectable in the buccal mucosa, reaching an average of about 1% of normal in all patients (approximately 0.3 to 0.6 U per unit of hexosaminadase A, with the normal level at 59 U per unit of hexosaminadase A). Leukocyte enzyme levels have also shown persistently higher levels during treatment (mean of 18%, 12% and 35% of normal at weeks 26, 52 and 104 respectively.

Safety

Adverse events

All 10 subjects had at least 1 adverse event, and at least one deemed to be study drug-related. Overall there were 960 adverse events reported in this study period; eight subjects experienced 32 serious adverse events, including 2 that resulted in death. Seven subjects had 33 adverse events reported as severe.

The most common adverse events reported as Preferred Terms using the COSTART coding during the study period were: rhinitis (10 subjects), pain, asthenia and fever (9 subjects each), and increased cough, abdominal pain, vascular disorder, and rash (8 subjects each).

The most common of the 33 severe adverse events reported as Preferred Terms using the COSTART coding during the study period were: bone disorder (including cervical cord compression and spinal deformities), apnea and vascular disorders, allergic reactions and headaches. Ten of these 33 severe events were judged to be definitely or possibly related to the study drug. Fourteen of these 33 severe adverse events were also serious adverse events.

Adverse events were also classified by having occurred on an infusion date after the start of the infusion or as having occurred in non-infusion days. The infusion day adverse events reported by most subjects were: rash, urticaria, allergic reactions and headaches and

adverse events with the greatest occurrences were: urticaria (97 events), rash, and angioedema.

All subjects were pre-medicated with diphenidramine intravenously before the laronidase infusion, and some subjects also received corticosteroids and nonsteroidal anti-inflammatory drugs. If a reaction occurred during an infusion, the rate of infusion was slowed or temporarily stopped, the dosage could temporarily be reduced, additional doses of diphenidramine or corticosteroids could be administered or other interventions could be performed.

Reviewer's comment: Approaches to prevent or treat an infusion reaction were so varied that guidelines for a label would be problematic. Planning a consistent approach dictated by the clinical condition of the subject would be helpful in orienting physicians in the management of such reactions.

Deaths

There were 2 deaths that occurred during the 152-week portion of the study.
Subject 008, age 7, died on ---------- after the Week 103 infusion, of apnea (respiratory arrest). Respiratory distress occurred during a flight for the Week 104 assessment, followed by respiratory arrest, without response to intubation and full CPR efforts. During the week prior to the event, the subject's mother noted nasal congestion and discharge, which were also noted during enzyme infusion on April 5, 2000. Autopsy findings indicated an apparent systemic viral illness with histologic evidence of an active lymphocytic myocarditis and patchy bronchiolitis. Subject 008 had a high antibody titer, including IgG specifically to laronidase, which persisted until the last assessment at week 100. Complement activation was seen at weeks 6 and 12, but not subsequently. Autopsy findings included mild immune complex deposits in glomerular basement membranes, and mild focal deposition of IgM in lung capillaries with minimal C3, but without any pathologic change by light or electron microscopy in either organ to suggest a functional effect. The subject's residual underlying MPS I disease may have contributed to death. This subject had received weekly infusion premedication with methylprednisolone starting at Week 8 and continuing throughout the study due to hypersensitivity-type reactions. Study drug did not appear to be directly implicated based on history and autopsy findings. The principal investigator and Sponsor considered the death to have an unlikely relationship to study drug.

Reviewer's comment: This death is more likely related to acute complications of a viral illness in a subject with severe manifestations of the disorder. It is difficult to discern the role of the elevated serum anti-IDU antibody titer, histopathological scenario and prior history of complement activation as a contributing factor.

Subject 002, age 13, died on ---------- after the subject's last study infusion at Week 137, of cardiac and respiratory arrest. This subject had a significant medical history of musculoskeletal disease at study enrollment, including scoliosis. On ----------, the subject was admitted to the hospital for posterior spinal fusion for worsening of her scoliosis from T5 to L4. Postoperatively, the subject was unable to move the lower extremities, and through additional testing and procedures, was diagnosed with

spinal cord injury and ascending quadriparesis. The level of paralysis continued to ascend and the patient was maintained on mechanical ventilation due to respiratory failure. Weaning from ventilation did not produce spontaneous respiratory effort. ----------. The subject died within 2 hours of discontinuation of ventilation. The Principal Investigator stated that, in her opinion, the worsening of scoliosis, ascending paralysis, and death due to respiratory arrest were not related to the study drug. This opinion was shared by the Sponsor.

Laboratory Abnormalities

Serum Chemistries: Most subjects had elevated serum levels of alkaline phosphatase at screening and pre-treatment. These levels generally decreased by week 8, although for some subjects levels declined and remained above normal for the study period. Subject 002 had an elevated serum LDH level at week 8, with other liver enzymes in the normal range, and the LDH returned to normal by week 10. This same subject was noted to have intermittent mild hypokalemia starting at week 46. Subject 009 had an episode of hepatitis, likely related to macrolide hepatotoxicity from week 26 until week 30.

Hematology: Several subjects had chronic anemia at pre-treatment and the indices related to red blood cell remained stable throughout the study period.

Antibody development

All subjects developed IgG antibodies to the laronidase product as detected by ELISA by week 6 or 12 of treatment. Serum antibody levels generally declined over time. Using a Western blot technique, the sponsor determined that the initial antibodies detected were directed against a 60 KD protein impurity. Specific immune responses to rhIDU were seen in 4 subjects by Western Blot. Subject 002 had transient specific antibodies from week 10 to 14; in the other 3 subjects the Western blot specific antibody titers declined over time.

IgG titer did not correlate with hypersensitivity-type reactions in these patients. For example, Subjects 001 and 005 had relatively low antibody titers but had significant periods of recurrent urticarial reactions. In addition, titers in these 2 subjects had declined rather than risen during the periods of hypersensitivity reactions. On the other hand, Subject 009 had no hypersensitivity-type reactions and yet had relatively high antibody titers to laronidase product.

There was no apparent correlation between IgG antibody titer to laronidase product and reductions in excess urinary GAG levels, liver or spleen size. These antibodies did not neutralize enzyme activity as tested when the subject's sera was added to rhIDU at pH 3.5 and 5.5 and compared to negative controls, when no serum was added, or positive controls, with highly neutralizing canine antibodies to laronidase.

Complement activation, as measured by the difference between the pre-and postdose levels of CH50 and either C3 or C4, was highest at Week 6 for Subjects 007 and 008, and highest at Week 12 for Subjects 002 and 009. Complement activation was greatly reduced or resolved by Week 26 and no apparent complement activation was seen at Week 52 in any patient. There was no correlation between complement activation and need to receive glucocorticoids as pre-medications for infusion or to manage hypersensitivity-type

reactions during infusions. There were no apparent effects of the immune responses on development of immune complex disease or on glomerulonephritis based on urinalysis and GFR results.

Summary

This uncontrolled Phase 1 study of laronidase in 10 subjects with MPS I was able to demonstrate bioactivity in clinical areas that correspond to large accumulation of GAG's such as the reticulo-endothelial system and the kidneys, resulting in substantial reductions of hepatosplenomegaly and excretion of urinary GAG's. The effect of laronidase on other endpoints of clinical significance to patients with MPS I was variable with a much smaller magnitude. Specifically, assessments related to cardiac function, muscle-skeletal, airway and central nervous system function suggested an overall favorable trend, but it is imperative to note that these data obtained from an open label uncontrolled study cannot provide support for laronidase efficacy in MPS I. All subjects had infusion associated reactions, which were mild or moderate. All subjects had antibodies to laronidase as assessed by ELISA, but specific anti-IDU antibodies were confirmed in 4 subjects. 2 deaths occurred during this study, but these seem to be unrelated to the study drug, and consistent with the natural history of the severe presentation of MPS I.

Study ALID-003

"A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Multinational, Clinical Study of Recombinant Human Alpha-L-Iduronidase in Patients with Mucopolysaccharidosis Type I"

Overview

This study was conducted under IND -------, according to protocol ALID-003-99. This is the only Phase 3, double blind, placebo-controlled, and randomized clinical trial conducted for this product to support a claim of efficacy and safety in the treatment of patients with MPS I. The study started on December 28, 2000 and was completed on September 6, 2001.

At the end of the 26-week study period, all subjects were offered participation in an open label extension study to continue treatment with laronidase for up to 72 weeks or until market approval of this product.

Protocol

Title and Amendments: "A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Multinational, Clinical Study of Recombinant Human Alpha-L-Iduronidase in Patients with Mucopolysaccharidosis Type I". Protocol ALID-003-99.

Design

This was a randomized, double-blind, placebo-controlled, multicenter, multinational study. The study was divided in 2 consecutive phases: a 2-week period to assess eligibility and obtain baseline parameters, and a 26-week treatment phase in which subjects are randomized to receive weekly laronidase or placebo.

Objectives

- Primary: assess treatment-related changes in parameters of physiological and functional importance to subjects with MPS I to support a claim of efficacy of laronidase in the treatment of these various conditions.
- Additional objective: pharmacokinetic assessment in a subset of study subjects and exploring changes in pharmacokinetic parameters over time.
- Safety: assess the incidence of adverse events, including laboratory parameters, vital signs, physical examination, cardiac parameters and immunogenicity.

Patients

Inclusion criteria:

- Both genders, and aged five years or older.

- Documented diagnosis of MPS I, confirmed by measurable clinical signs and symptoms of MPS I, and a documented fibroblast or leukocyte α-L-iduronidase enzyme activity level of less than 10% of the lower limit of the normal range of the measuring laboratory.
- Negative pregnancy test (urine β-hCG) for female subjects of childbearing potential at baseline and use effective contraception throughout the study. Sexually mature males also must use effective contraception.
- Capable of standing independently a minimum of six minutes and walking a minimum of five meters within six minutes.
- Capable of performing a reproducible FVC maneuver.
- baseline FVC value that is less than or equal to 80% of his/her predicted normal FVC value based on Polgar predicted values for standing height for children five through seven years of age and the Hankinson predicted values for patients aged 8 and above.

Exclusion criteria:

- Prior tracheostomy.
- Prior bone marrow transplantation.
- Pregnant or lactating.
- Use of an investigational drug within 30 days prior to study enrollment.
- Medical condition, serious intercurrent illness, or extenuating circumstance that may significantly interfere with study compliance.
- Known hypersensitivity to laronidase or to components of the active or placebo test solutions.

Treatment assignment / Randomization

Eligible subjects were randomized to the laronidase or placebo group according to a central randomization scheme. The randomization had a block design to ensure balanced allocation to both treatment arms within each clinical site. All subjects, investigators, site personnel, and members of the sponsor's staff were masked to the treatment assignment. The computer-generated randomization codes were held by Genzyme Corporation.

Product information and administration

Subjects randomized to the treatment group received laronidase at a dose of 100 U / kg intravenously weekly during the treatment phase for 26 weeks. Subjects randomized to placebo receive a pH-adjusted, phosphate-buffered solution. Study solutions were infused weekly, with a minimum interval between consecutive infusions being 4 days.

For administration to subjects, the laronidase or placebo were diluted with between 100 mL to 250 mL (depending on the subject's weight) of 0.1% human serum albumin in saline.

All subjects were pretreated 30 minutes to one hour prior to infusion with an antipyretic regimen (acetaminophen or ibuprofen) and an antihistamine regimen (diphenhydramine, hydroxyzine, chlorpheniramine, cetirizine, fexofenadine or loratadine).

The initial infusion rate of 0.01 mg/kg (2 U/kg) of body weight per hour for 15 minutes was incrementally increased if well tolerated to a maximum of 0.25 mg/kg (43 U/kg) of body weight per hour to deliver the total volume of the infusion over approximately 4 hours. The total infusion volume for subjects weighing between 5 and 20 kg was 100 mL and for subjects weighing between 21 and 100 kg was 250 mL. During the first hour of infusion, a total of 4 infusion rate increases were allowed (once every 15 minutes) if there was no clinically relevant change in vital signs or any indication of an infusion-associated reaction. Subjects were observed for safety for up to 3 hours after the completion of each intravenous infusion. Subjects were required to stay for a longer observation period at the Investigator's discretion. During the 26-week infusion phase, again at the discretion of the Investigator, placement of an indwelling intravenous catheter in a study patient was allowed if warranted due to difficulties in achieving intravenous access for the weekly study-solution infusions.

If a patient was unable to receive a scheduled treatment infusion within the 10-day maximum period allowed following the last scheduled infusion, that patient received a treatment infusion at the earliest possible date. After such an out-of-schedule treatment infusion, the next infusion was given within 7 ± 3 days. Subsequent treatment infusions were given according to the original weekly treatment infusion schedule.

Evaluations

a. Forced Vital Capacity (FVC), at baseline and at Weeks 4, 8, 12, 16, 20, and 26.
b. Six-minute walk distance, reported in meters walked, at baseline (3 times, the third being considered the baseline measurement) and at Weeks 4, 8, 12, 16, 20, and 26. Heart rate, respiratory rate, and oxygen saturation were to be measured prior to start, immediately following, and 2 minutes following the completion of the six-minute walk.
c. Children's Health Assessment Questionnaire (CHAQ) for subjects 5 –18 years of age or Health Assessment Questionnaire (HAQ) for subjects 19 years of age or older are assessed at baseline, and weeks 4, 12, and 26
d. Sleep study (to measure apnea/ hypopnea events and oxygen desaturation) are assessed at baseline, and weeks 4, 12, and 26
e. Liver volume by MRI at baseline and week 26
f. Urinary Glycosaminoglycans (GAG) at baseline and at weeks 4, 8, 12, 20, and 26
g. Joint Range of Motion at baseline and weeks 12 and 26
h. Quality of Life (Child Health Questionnaire or SF-36) at baseline and weeks 12 and 26
i. Resource utilization at baseline and at weeks 4, 8, 12, 20, and 26

j. Standing heights for measurement of growth velocity at baseline and at weeks 4, 8, 12, 20, and 26

k. Investigator global assessment at week 26

l. Visual acuity by standard eye chart testing, ocular pressure, corneal clouding, and retina / optic nerve exam at baseline and week 26

m. EKG and echocardiogram at baseline and week 26

n. FEV_1, total lung capacity and diffusing capacity at baseline and week 26

o. Parent/caregiver quality of life at baseline and week 26

p. Pharmacokinetic assessments at 2 selected sites for all enrolled subjects at those sites at week 1, 12 and 26, with samples collected at pre-dose, 15, 45, 90 minutes of infusion, 3 and 4 hours of infusion, 10, 30, 45, 60 minutes post-infusion, 2, 3, 4 and 6 hours post-infusion.

q. Medical history, VS, and physical examination, at baseline, and at weeks 4, 12 and 26

r. Brain / cranio-cervical junction MRI at baseline (all subjects) and at the investigator's discretion at week 26

s. Laboratory evaluations at baseline and weeks 4, 12 and 26, including clinical chemistry, hematology and urinalysis. Urine pregnancy test for females of childbearing potential at baseline and every 4 weeks.

t. Antibody testing at baseline and every 4 weeks. Complement activation (CH100 or CH50 and C3 or C4 components) was measured if symptoms of a hypersensitivity reaction are noted.

u. Adverse events

Safety Monitoring

An independent Allergic Reaction Review Board (ARRB) was created to review signs of moderate or severe hypersensitivity and provide guidance on management of these reactions. The ARRB interacted with the Genzyme Pharmacovigilance group and infrequently directly with investigators.

Endpoints

- Primary efficacy:

a. Mean change from baseline to week 26 in the percent predicted FVC value based on standing height

b. Mean absolute change from baseline to week 26 in the 6 minute walk (in meters)

- Secondary efficacy:

a. Apnea / Hypopnea Index

b. Hepatomegaly

c. Disability Index of the Children's Health Assessment Questionnaire (CHAQ) / Health Assessment Questionnaire (HAQ)

d. Shoulder flexion

- Tertiary Efficacy:

a. QoL (from Child Health Questionnaire given to children 5 to 18 years old or the Short Form – 36 given to adult subjects)

b. Pain scores from the Children's Health Assessment Questionnaire (CHAQ) / Health Assessment Questionnaire (HAQ)

c. Urinary GAG

d. Growth Velocity for pre-pubertal subjects

e. Visual Acuity

f. Cardiac Function Testing by electrocardiogram and echocardiogram parameters

g. Investigator Global Assessment

h. Forced Expiratory Volume in One second (FEV1)

i. Total Lung Capacity

j. Diffusing Capacity

k. Parent / Primary Caregiver QoL

l. Resource Utilization defined as event-based hospital data, home health care, therapist visits, MPS I medications, and related medical equipment, outpatient consultations, time lost from work or school activities due to MPS I for patients and caregivers

Reviewer's comment: The primary efficacy endpoint of percent predicted FVC was modified to include different formulas to calculate the variable according to age categories (Polgar for ages 5 – 7 years and Hankinson for subjects 8 years of age or older at baseline). The percent predicted FVC was again revised after the study conclusion to be calculated in the context of baseline height, instead of the current height at the time of spirometry assessment at week 26. Secondary and tertiary endpoints were modified as follows:

The sleep study endpoint was clarified further to include measures of electroencephalogram, electromyogram, nasal and oral airflow, chest and abdominal movement, oxygen saturation, and rapid eye movement. The data would be transferred to a core laboratory at New York University and interpreted in a blinded fashion. The independent expert performing the blinded readings noted a substantial proportion of subjects with normal AHI scores at baseline and recommended a subset analysis of the most severely affected subjects (AHI scores = 10 for children younger then 15 years and AHI scores = 15 for subjects older than 15 years) and for all subjects with AHI = 20, in whom clinical intervention may be warranted.

Visual Acuity was further expanded to included assessments of tonometry, fundoscopy and slit lamp examinations.

Statistical Analysis

Sample size was estimated based on the cross-sectional survey study ALID-004 data in MPS I subjects. A total sample of 42 subjects (21 per treatment group) provided 80% power to detect an absolute difference of 15% from a value of 55% in mean percent predicted FVC from baseline to week 26, assuming a standard deviation of 15% and a dropout rate of 20% and maintaining a Type I error at 5%. The same total sample size provided 80% power to detect a difference of 125 meters in the mean distance walked comparing baseline to week 26, assuming a standard deviation of 15% and a dropout rate of 20% and maintaining a Type I error at 5%.

The final statistical analysis plan was submitted on 9/19/01, 13 days after conclusion of the study. Genzyme was responsible for data entry and editing, review of information in the CRF's, statistical analysis (except QoL data, performed by an external consultant) and generation of the clinical study reports.

Primary efficacy endpoints are analyzed for both the Intent to Treat (ITT) population and the Per Protocol (PP) population. ITT population includes all randomized subjects and is the basis for the efficacy determination. Per Protocol population is defined as all subjects who received at least one infusion and had no major protocol violations, e. g. missing more than 5 of the 26 total infusions. Hypothesis testing is done using Wilcoxon rank-sum test on the change from baseline to week 26 in the 2 treatment groups for both primary endpoints. Baseline is defined as the third or final evaluation during the baseline phase just prior to randomization. This is due to a potential training effect of performing 3 assessments for FVC and 6 minutes walk distance in a 2-week period.

The study would be considered statistically significant if both primary endpoints meet or exceed the critical p value of 0.05 in the difference between the treatment groups. In addition, descriptive statistics is used for both the ITT and PP populations to present changes from baseline to all timepoints in the study, by treatment group.

Secondary and tertiary endpoints are tested for the ITT population using ANOVA, with treatment group and study site as independent variables and mean change from baseline for each continuous secondary and tertiary endpoint as the dependent variable, except for the Investigator Global Assessment, which is intrinsically a categorical comparison to baseline. In addition, descriptive statistics is used for the ITT population to present changes from baseline to all timepoints in the study, by treatment group. Categorical tertiary endpoints are analyzed with Fisher's Exact test.

Missing data for subjects who missed study visits or terminated the study early are imputed by the last observation carried forward method, except for safety data or resource utilization data, which are not imputed.

Study Conduct

The study was conducted under IND 7334. Study sites were audited by representatives of Genzyme Corporation or Genzyme Europe for North America or European sites, respectively.

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Study conduct changes:

- ELISA was used for IgG screening in the original protocol. Samples testing positive were confirmed by radioimmunoprecipitation at Genzyme Corporation Immunology, rather than the Western Blot assay used in the Phase 1 study.
- Amendment 3 submitted on 3/27/01 (3 months into the study) revises and expands on the allowed antihistamines and antipyretics to be used prior to infusion.
- Amendment 3 also revises the method to determine the predicted FVC values according to the age of the affected subject: Polgar predicted values for children 5 to 7 years old and Hankinson predicted values for subjects 8 years and older.

Reviewer's comment: This last change has no effect in the data collection of FVC, as the calculation of the predicted FVC value for the purpose of the analysis is not performed at the time of the assessment.

Database Integrity

All data were collected in CRF's provided to investigators by Genzyme. Representatives of BioMarin/ Genzyme LLC monitored the study progress in all sites according to ICH-GCP guidelines. CRF's were returned to Genzyme for data entry into a study database for analysis and reporting. All data captured electronically (e.g. laboratory data) was electronically transferred to the database. Upon completion of the data entry, the database received a quality assurance check. Prior to locking the database, all data editing was completed and decisions regarding evaluability of all subject data in the statistical analysis were made. The rationale for excluding any data from statistical analyses was prospectively defined. The statistical analysis did not begin until the entire ----------database was locked and signed off.

After completing the final study report for ALID-003 on February 17, 2002, it was ascertained that the joint range of motion variables had been incorrectly assessed at several sites. To maintain the integrity of the database, the joint range of motion measurements were corrected in the database. The tables, figures, and patient data listings that were affected by these changes were recreated. Where summary numbers cited in the study report text were affected, the report was updated. The study report was reissued on June 21, 2002, with all affected components updated.

Reviewer's comment: The study report does not specify the date of the database locking and the date when statistical analysis began. The changes described above did not lead to any important changes in the conclusions of the study.

Protocol violations

Protocol violations were prospectively defined prior to locking the database as follows:

- subject missing more than 5 of the 26 infusions
- occurrence of a treatment dispensing error with the subject receiving the incorrect drug assignment
- tracheostomy performed in a subject during the study
- bone marrow transplantation performed in a subject during the study
- occurrence of infusion associated reaction classified as severe by the investigator

There were numerous protocol deviations in all clinical sites. However, these deviations did not impact the overall safety evaluation. The majority of the deviations were related to timing of infusion or assessments, or incomplete performance of the required assessments at a given timepoint. Deviations occurring in 2 subjects were considered major protocol violations that could impact in the efficacy analyses; these subjects were excluded from the PP analysis. The violations were: presence of a significant medical condition (prior heart transplant and pacemaker implant) in a subject randomized to placebo and missing 7 of the 26 infusions in a subject randomized to laronidase. These subjects were included in the ITT analyses.

FDA site inspection findings

The FDA inspector for the Canadian and United Kingdom sites noted that either the Polgar normative method (irrespective of the subject's age) or a non-specified method were used in calculating the percent of predicted Forced Vital Capacity (FVC). The only % FVC values generated at the clinical sites were those used in the determination of eligibility to the study.

In addition, the FDA site inspector for the University of North Carolina Department of Pediatrics uncovered discrepant information for 5 subjects related to recording of FVC (in liters) from the pediatric pulmonary lab and the data recorded in the CRF for the week 26 visit. The sponsor explained in a November 19, 2002 teleconference that all values for the pulmonary testing to be recorded in the CRF were supposed to originate from the testing performed at the pediatric pulmonary lab. In the North Carolina site, the diffusing capacity and total lung capacity data had to be obtained in the adult pulmonary laboratory, which also generated redundant data related to FVC and FEV1. The five subjects had their FEV1 and FVC data obtained in the adult pulmonary laboratory entered in the CRF erroneously. These data were used in the analyses. The sponsor generated an Erratum containing the FEV1 and FVC values from the pediatric pulmonary laboratory and re-analyzed the primary endpoints in the study. The results of the correct FVC and % predicted FVC were also included in this BLA review, and were indicated as such.

Results

Subject disposition

The study started on December 28, 2000 and was completed on September 6, 2001. 47 subjects with MPS I enrolled into the study. Two of these failed to meet the entry criterion of reproducible FVC measurements and were excluded prior to randomization. The remaining 45 subjects were randomized on a 1:1 ratio to either treatment group. Of the 45 subjects, 22 were randomized to laronidase and 23 were randomized to placebo. All 45 subjects completed the study and their data were included in the safety and efficacy reports. The 45 subjects were enrolled in 5 centers, as follows:

- Dr. Wraith (UK): 12 subjects, being 6 laronidase
- Dr. Beck (Germany): 9 subjects, being 4 laronidase
- Dr. Muenzer (North Carolina): 6 subjects, being 3 laronidase
- Dr. Kolodny (New York): 7 subjects, being 3 laronidase
- Dr. Clarke (Canada): 11 subjects, being 6 laronidase

Baseline characteristics

Important baseline characteristics for understanding the treatment groups are shown in Table 6.

Table 6. Baseline characteristics of selected parameters

Baseline Characteristic	Category	Placebo n = 23	Laronidase n = 22
Gender	Male	11	11
	Female	12	11
Race	Caucasian	21	16
	Black	0	0
	Hispanic	0	4
	Asian	1	1
	Other	1	1
Age Group	6 - 12 years	10	12
	13 to = 18 years	8	3
	19 to = 65 years	5	7
Syndrome	Hurler	1	0
	Hurler-Scheie	19	18
	Scheie	3	4
Years since onset of symptoms	Mean ± SD	12.7 ± 7.7	12.7 ± 8.5
Years since initial diagnosis	Mean ± SD	8.7 ± 6.1	9.4 ± 6.6
Enzyme activity (% lower normal range)*	Mean ± SD	1.9 ± 3.2	1.2 ± 2.1
Weight (kg)	Mean ± SD	40.3 ± 13.0	35.3 ± 12.4
Height (cm)	Mean ± SD	137.2 ± 12.1	133.5 ± 16.1

* Enzyme activity as assessed in skin fibroblasts or leukocytes

Table 7 shows the baseline characteristics for the 2 co-primary endpoints: % FVC and 6 minute walk distance.

Baseline Characteristics	Placebo n = 23	Laronidase n = 22
Mean % Predicted FVC	54.2 ± 16.0	48.4 ± 14.8
Mean 6 min. walk distance (m)	366.7 ± 113.7	319.0 ± 131.4

Study drug exposure

All 45 randomized subjects completed 26 weeks of the study. The mean (± SD) number of study drug infusions for the placebo group was 25.4 ± 0.9 whereas for the laronidase-

treated group was 25.3 ± 1.6 infusions. One subject in the laronidase group missed 7 infusions, but 6 of these were due to a hospitalization for aortic stenosis. The most common reasons for missing infusions were similar for placebo and laronidase and related to problems in travel arrangements or illness.

Primary endpoints

Percent Predicted Forced Vital Capacity (% FVC)

Primary analysis

Lung volumes (measured in Liters) vary greatly among individuals due to extra-pulmonary factors, such as age, height, race and gender. In order to account for these variations and increase interpretability of the data, the sponsor proposed the use of % FVC. % FVC is usually calculated based on the subject's height at the time of assessment of the pulmonary function.

After the breaking of the blind, and during a presentation of the %FVC data to investigators in the Phase 3 double blind study, a discussion on the issue of how appropriate the use of the current height was in the computation of % FVC ensued. Three arguments in favor of using baseline height in the calculation of % FVC were used:

- Height is difficult to measure in subjects with MPS I due to skeletal and joint disease, with intra-subject variability
- If changes in joint stiffness and posture were more prevalent in the laronidase-treated group, this would lead to a systematic reduction in the apparent effect of laronidase on % FVC
- Conversely, placebo-treated subjects had a 2.7 % decrease in the % FVC calculated based on current heights without any change in lung volumes. A more accurate interpretation of lung volumes changes can be achieved when the normalized values (expressed as percent of predicted values) are calculated using baseline height.

Assessments for all subjects at baseline and week 26 were completed. Therefore no imputation for missing data was necessary. Table 8 shows the changes from baseline to week 26 in median and mean % FVC, as calculated using both the current height at the time of assessment or using the baseline height, for both treatment groups.

Table 8. Changes from Baseline (± SD) to Week 26 in median and mean % FVC

% FVC	Laronidase	Placebo	p value
Mean Baseline	48.4 ± 14.8	54.2 ± 16.0	
Mean Week 26 (Baseline Height)	53.7 ± 18.6	53.3 ± 14.2	
Mean Change (Baseline Height)	5.3	- 0.6	
Mean Difference between groups	5.9		
Median Change (Baseline Height)	3.0	0.0	0.016 *
Mean Week 26 (Current Height)	50.2 ± 17.1	51.5 ± 13.1	
Mean Change (Current Height)	1.8	- 2.7	
Mean Difference between groups	4.5		
Median Change (Current Height)	1.0	- 1.1	0.028 *

*Wilcoxon test

Reviewer's comment: As discussed above regarding the use of current height at week 26 or baseline height in the computation of % FVC, the data on height for the placebo-treated group shows only a modest increase from a mean (± SD) of 137.2 (± 12.5) cm to 139.0 ± 11.6, a mean change of 1.8 cm in 26 weeks of study. In contrast, the mean laronidase-treated group increased the mean height from 133.5 ± 16.1 to 136.5 ± 15.4 cm, a mean change of 3 cm in the 26 weeks of the study.

In addition to the statistical significance for the treatment effect between the 2 groups, the sponsor also cites the 11% relative improvement in the laronidase (5.3 % / 48.4 %) compared to baseline, a clinically significant improvement according to the American Thoracic Society.

The FDA inspection in Site 4 (University of North Carolina) uncovered discrepant information for 5 subjects related to recording of FVC (in liters) at week 26. In addition to the FVC measured in the pediatric pulmonary lab these subjects also had complete pulmonary function testing at the adult pulmonary laboratory (which also included a redundant FVC assessment). FVC data from the adult pulmonary lab, rather than from the pediatric lab, was entered in the CRF erroneously for the Week 26.

Table 9 shows the mean (± SD) results of % FVC in placebo and laronidase-treated subjects using baseline heights and computed with the 5 values corrected in Site 4.

Table 9. Changes from Baseline (± SD) to Week 26 in median and mean % FVC

% FVC	Laronidase (n=22)	Placebo (n=23)	p value
Mean Baseline	48.4 ± 14.8	54.2 ± 16.0	
Mean Week 26 (Baseline Height)	53.3 ± 18.5	53.5 ± 14.1	
Mean Change (Baseline Height)	4.9	- 0.7	
Mean Difference between groups	5.6		
Median Change (Baseline Height)	3.0	0.0	0.009 *

*Wilcoxon test

Reviewer's comment: Even as the statistical analysis shows a statistically significant treatment effect for laronidase, the clinical significance of the effect size is unclear. Forced Vital capacity has been chosen as a surrogate for the restrictive component of the pulmonary impairment, but may not reflect the entire spectrum of impairment seen in other areas of lung and upper airway function. The fact that eligibility for this trial was restricted to subjects with impaired lung function (less than 80% of predicted normal FVC) would be expected to improve the chances of demonstrating a larger clinical effect, as compared to a lessened treatment effect that might be seen if subjects with healthier FVC's were also enrolled.

The 95 % confidence interval for the difference between groups in change of % FVC from baseline to week 26 is 0.9 – 8.6 %.

Exploratory Analysis

Prospectively Defined Exploratory Analysis

Analysis of covariance was performed and has shown the retention of the treatment effect when covariates such as clinical site, baseline FVC, baseline Apnea Hypopnea Index, baseline Total Lung Capacity, baseline liver volume, and baseline GAG level are taken into account (p= 0.04). The ANCOVA was performed using the % FVC as calculated using the current height.

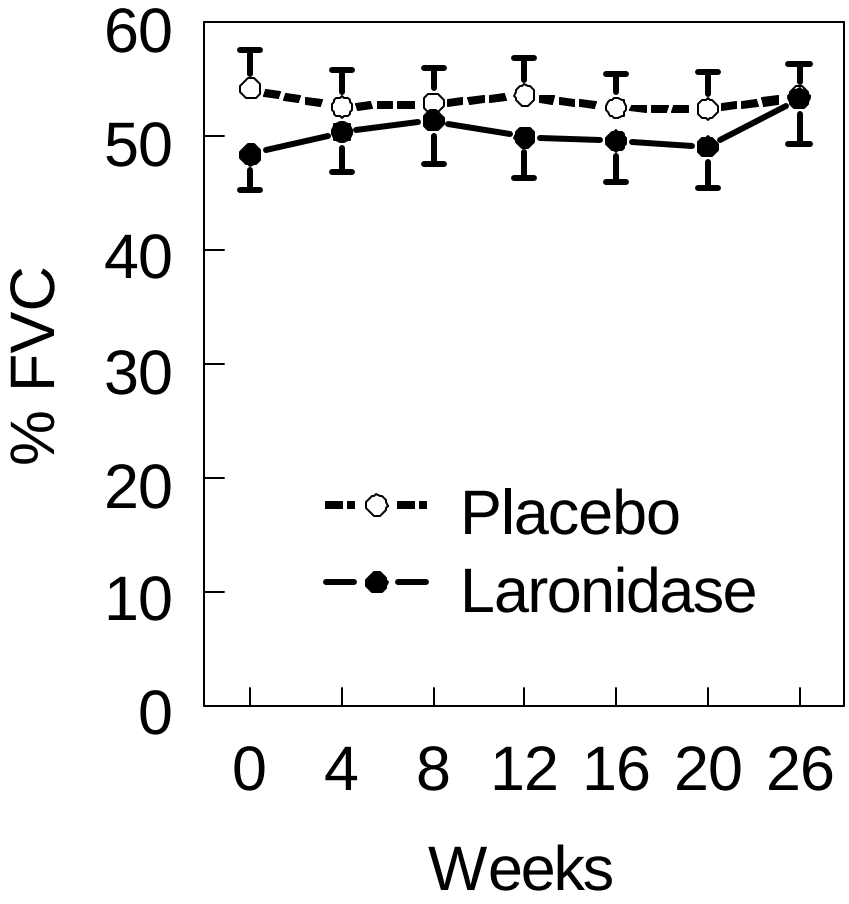
Post-hoc Exploratory Analysis

Analysis of Forced Vital Capacity, independently of subject's age or height:

The laronidase-treated group had a mean (± SD) increase in forced vital capacity of 0.10 (± 0.14) L, whereas the placebo-treated group had no change in the mean forced vital capacity (- 0.02 ± 0.12 L) ($p < 0.01$, as analyzed by the Wilcoxon test). When analyzing the relative change in liters of forced vital capacity from baseline to week 26, the laronidase-treated group had a mean (± SD) increase of 11.2 (± 21.1) % increase, whereas the placebo-treated group had a mean increase of 1.4 (± 17.6) % in forced vital capacity ($p = 0.02$, by Wilcoxon test).

Analysis by Study Visit:

Figure 2 demonstrates the effect of laronidase treatment on the % FVC, as calculated based on baseline heights, across the study period, compared to control.



Note: 4 missing values for Week 4 were imputed by LOCF.

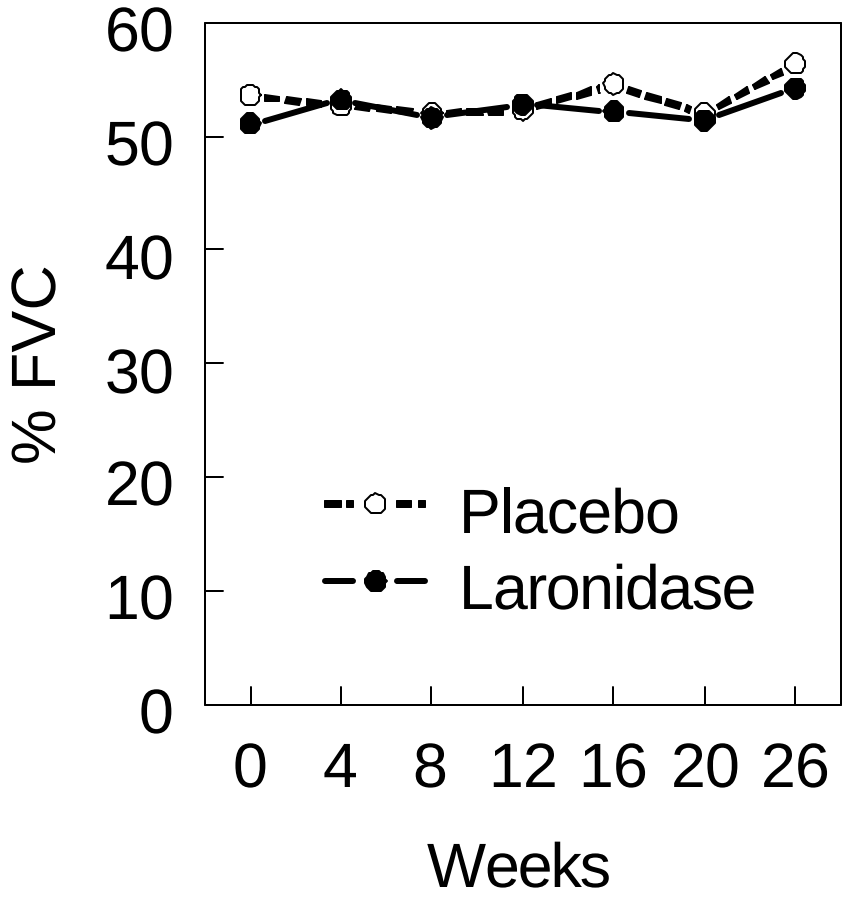
Mean % FVC was lower in the laronidase-treated group compared to placebo at week 0. From baseline to week 4 a tendency to converge the lines for the 2 treatment groups is seen. While the placebo-treated subjects had a relatively constant mean % FVC for the remainder of the study, laronidase-treated subjects had a mean % FVC small drop from week 8 to week 20. There was a tendency for the 2 curves to converge by the end of the 26 week study period, primarily because of a rise of % FVC's in the laronidase-treated group between weeks 20 and 26.

Reviewer's comment: The sponsor explains the drop in % FVC seen between weeks 8 and 20 in the laronidase-treated group as possibly related to a combination of various factors, including intercurrent illness, assessment following an infusion, seasonal effects or subject fatigue from repeat study visits. However, given the size of the sample and the homogeneous distribution of disease severity in the 2 treatment groups, one would expect to observe the same factors playing a role in the control arm. Two subjects in the

laronidase-treated group had significant worsening in the % FVC between weeks 12 and 20, not explained by a correlation with AE's or use of concomitant medications. The rise in % FVC between week 20 and week 26 in the laronidase-treated group is remarkable. Three laronidase-treated subjects had a substantial rise in % FVC in that time period. Subject 30608 manifested an increase from 59.4 % to 80.6 % of the normal predicted FVC, without an obvious explanation; Subject 30806 increased % FVC from 40 % to 53.7 %, which could be explained on the basis of recovery from a series of SAE's, starting with severe CHF diagnosed at week 12, secondary to severe aortic stenosis, complications of aortic valvuloplasty, with cardiac arrest, pneumonia and sepsis; and Subject 61010 also had an unexplained significant rise in % FVC from 17 to 30.9 %. Most of the other laronidase-treated subjects experienced modest improvements in % FVC in the interval between weeks 20 and 26. On the other hand, the placebo-treated group had a remarkable but unexplained drop in the % FVC from Baseline to week 4, with subsequent stabilization of % FVC's until week 26. The drop cannot be attributed to a training effect during the 3 baseline assessments made because it was not observed in the laronidase group. Placebo-treated Subject 60603 had a substantial drop from baseline to week 4 in the order of 23 points in the %FVC (clearly an outlier for both groups in the magnitude of drop). A sensitivity analysis excluding this subject maintains the treatment effect seen (6.4 %) with a p = 0.04. However, comparing the change from baseline to week 26 in the laronidase-treated group and the change from week 4 to week 26 in the placebo-treated group (in other words, considering week 4 as the "baseline" for the placebo-treated group) would eliminate the treatment effect observed in the ITT population, with a difference from placebo of 2.46 % (p=0.22).

Another way to depict the variations of % FVC in both treatment groups is to show the medians for each timepoint in which % FVC was assessed. The resulting figure (Figure 3) is similar to Figure 2, except that the placebo group had a median drop from week 16 to week 20, and also exhibited a rise from week 20 to week 26, similar to that seen in the laronidase-treated group.

Figure 3. Effect of laronidase treatment on the median % FVC across the study period



Analysis by Study Center: There was general consistency in study outcomes for this endpoint. In 4 of the 5 clinical sites, placebo-treated subjects experienced worsening of the % FVC and rhIDU-treated subjects showed improvement in this primary endpoint. In one center (Canada), the laronidase-treated subjects did not show improvement of % FVC, whereas placebo-treated subjects did.

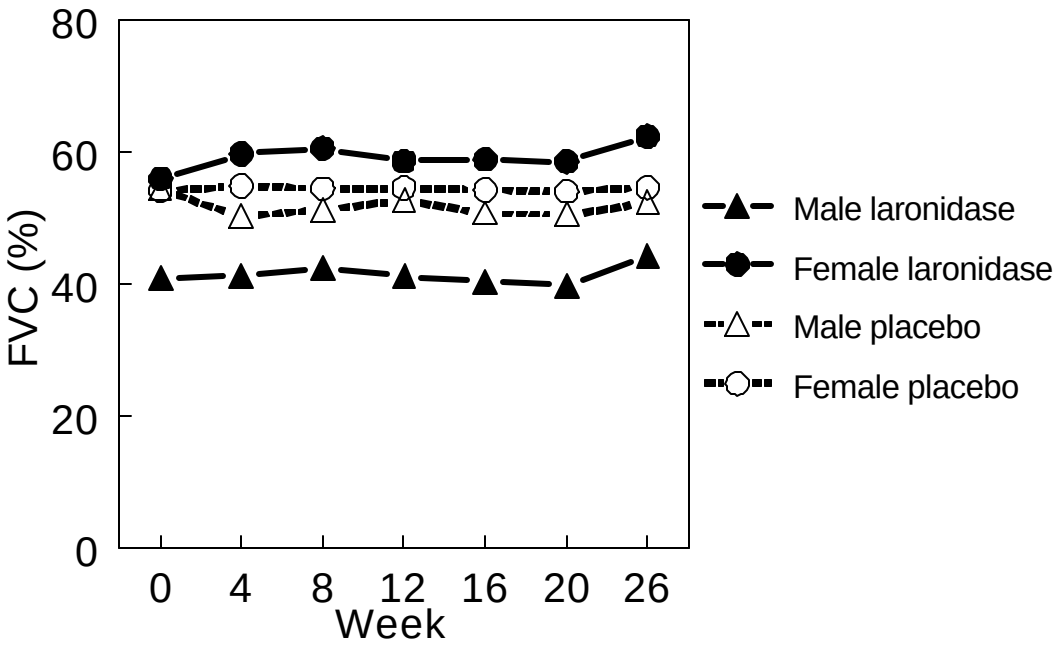
Analysis by Gender: Table 10 shows the mean (± SD) baseline and changes from baseline to week 26 in % FVC by gender.

Table 10. Mean % FVC baseline and changes from baseline to week 26 according to gender

Gender	Placebo				Laronidase			
	n	Baseline	Week 26	Change	n	Baseline	Week 26	Change
Female	12	54.1 ± 13.1	54.6 ± 12.2	0.5	11	55.9 ± 9.9	62.3 ± 17.6	6.4
Male	11	54.4 ± 19.4	52.3 ± 16.5	- 2.1	11	40.9 ± 15.5	44.2 ± 15.2	3.3

Reviewer's comment: The treatment-associated difference in change from baseline was similar across the genders, but males in both treatment groups fared worse than females in the same treatment groups. It is notable from data shown in Table 10 that laronidase-treated males had worse mean % FVC at baseline and at week 26 compared to the other subgroups.

Figure 4. Mean % FVC across the study visits plotted by gender and treatment groups



Reviewer's comment: As depicted in Figure 3, most of the drop between baseline and week 4 in mean % FVC seen in the placebo group comes from males in the group, and most of the increase in mean % FVC seen in the laronidase group for the same period comes from females in that group. The increase in mean % FVC seen between weeks 20 and 26 in the overall laronidase group comes from both males and females.

Analysis by Age Category: Table 11 shows the mean % FVC at baseline and change from baseline to week 26 in the 2 treatment groups across 3 different age categories: children between 6 and 12 years inclusive, subjects between 13 and 18 years inclusive, and those 19 years and older.

Table 11. Mean % FVC baseline and changes from baseline to week 26 according to age category.

Age category	Placebo			Laronidase		
	n	Baseline	Week 26	n	Baseline	Week 26
6 - 12	10	62.1 ± 11.6	59.6 ± 12.0	12	51.5 ± 14.9	58.1 ± 20.4
13 – 18	8	44.1 ± 17.1	46.6 ± 14.9	3	44.5 ± 8.4	46.8 ± 7.0
19 – 43	5	54.8 ± 15.3	52.3 ± 14.1	7	44.8 ± 17.4	47.6 ± 17.6

Reviewer's comment: Approximately half of the subjects were younger than 12 years, and in these, laronidase had a more significant impact with a difference from placebo of 9 %. Other age subgroups had few subjects and no clear trend could be demonstrated.

Analysis by Race / Ethnicity: The great majority of subjects were Caucasian, and no meaningful comparisons were possible among the races to examine the treatment effect.

Analysis by impairment of FVC at baseline: This analysis was conducted between 2 subsets in each treatment arm: the subjects above the median value for % FVC at baseline and the subjects whose % FVC fell below the aggregate median value at baseline (51.4 %). Table 12 shows the mean % FVC at baseline and change from baseline to week 26 in the 2 treatment groups in the milder and more severe categories.

Table 12. Mean % FVC baseline and changes from baseline to week 26 according to baseline % FVC severity

% FVC Impairment	Placebo			Laronidase		
	n	Baseline	Week 26	n	Baseline	Week 26
= 51.9 %	13	65.6 ± 8.6	63.0 ± 10.0	10	60.3 ± 6.9	68.1 ± 13.3
< 51.9 %	10	39.5 ± 10.0	41.1 ± 7.4	12	38.4 ± 12.0	40.8 ± 11.7

Subjects with milder pulmonary disease at baseline by this criterion did significantly better than subjects with lower FVC at baseline (p=0.04) with a 10.4 % difference from placebo in the milder pulmonary severity subset compared to 0.8 % difference from placebo in the most severely affected individuals at baseline.

Reviewer's comment: This observation suggests that the laronidase effects on GAG's accumulation in airways and parenchymal lung tissue can be more easily distinguished from that of the control arm when irreversible structural changes did not take place yet. The apparently stronger laronidase effect seems to be also evident in the analysis of these FVC data by age category, if one assumes that children, as a group of mostly MPS IH-S, would have had less time to develop fibrosis or other inflammatory elements. One needs to keep in mind that % FVC is mostly an index of pulmonary function, but

other parameters, such as liver volume could have significant impact on the amount of restriction being assessed. Hepatosplenomegaly, as seen in both the Phase 1 study as well as in the present study (see below) is reduced in the laronidase-treated group.

Table 13 shows the mean changes from baseline to week 26 in the % predicted FVC among the 4 quartiles of baseline severity in % FVC.

Table 13. Mean changes (± SD) from baseline to week 26 in % FVC by the quartiles of impairment at baseline

Impairment level	range % FVC	Laronidase	n	Placebo	n
least ↓ most	77.4 – 65.4	10.4 ± 8.6	4	-3.1 ± 3.2	7
	65.4 – 51.9	6.1 ± 8.6	6	-1.8 ± 8.8	6
	51. 9 – 41.6	0.7 ± 10.5	6	0.7 ± 3.8	5
	41.6 – 15.5	4.2 ± 6.5	6	3.9 ± 5.3	5

Reviewer's comment: In the laronidase-treated group, there is a trend towards greater improvement in % FVC among the less severely affected subjects. It suggests also that laronidase has little benefit in subjects more advanced pulmonary restriction.

Analysis of subject distribution according to gender, age category, treatment assignment and impairment of % FVC at baseline

As seen from the data on % FVC changes in the 2 treatment groups by age category and gender, these demographic factors influenced the treatment effect on this primary endpoint. It is important to investigate whether clusters within a certain age category were more prevalent in males or females. Table 14 shows the age categories for male and female subjects in this study 003 at baseline, with the treatment allocations within the gender and age categories.

Table 14. Distribution of subjects by age categories and gender.

Gender	Age Category (years)	Treatment (n)	
		Laronidase	Placebo
Female	6 - 12	8	5
	13 – 18	1	3
	19 - 43	2	4
Male	6 - 12	4	5
	13 – 18	2	5
	19 - 43	5	1

These data show that the numbers of subjects in each age category were relatively similar for both genders, so that any effect of each of these demographic characteristics (age and gender) on the outcomes of the study can be separately identified.

Similarly, because of the effect of pulmonary restrictive disease impairment at baseline, it is important to analyze the distribution of subjects by gender according to the impairment of % FVC at baseline (Table 15)

Table 15. Distribution of subjects by gender and % FVC impairment at baseline.

Gender	Impairment of % FVC	Treatment (n)	
		Laronidase	Placebo
Female	77.4 – 65.4	3	3
	65.4 – 51.9	4	3
	51.9 – 41.6	3	4
	41.6 – 15.5	1	2
Male	77.4 – 65.4	1	4
	65.4 – 51.9	2	2
	51.9 – 41.6	3	2
	41.6 – 15.5	5	3

There are more males with more impaired % FVC at baseline than females. 8 males had the most severe quartile of % FVC compared with 3 females. As noted before, male gender and more severe disease are associated with the least effect of laronidase on % FVC. However due to the imbalanced distribution of subsets, one cannot conclude that gender and baseline severity in % FVC played separate roles in the limited laronidase effect in these subsets.

We can analyze the distribution of subjects according to both impairment of % FVC at baseline and age categories, shown in Table 16.

Table 16. Distribution of subjects by age categories and impairment of % FVC at baseline.

Impairment of % FVC	**Age Category (years)**	**Treatment (n)**	
		Laronidase	Placebo
77.4 – 65.4	6 - 12	3	4
	13 – 18	0	1
	19 - 43	1	2
65.4 – 51.9	6 - 12	4	3
	13 – 18	1	1
	19 - 43	1	1
51.9 – 41.6	6 - 12	3	3
	13 – 18	0	2
	19 - 43	3	1
41.6 – 15.5	6 - 12	2	0
	13 – 18	2	4
	19 - 43	2	1

More subjects younger than 12 years have less severe % FVC at baseline than older subjects. However equal numbers of adult subjects had the most and least severe pulmonary restrictions at baseline. Therefore the association is not as strong as between gender and impairment of % FVC at baseline, shown in Table 15. It is possible that age and baseline impairment had independent influences over the effect of laronidase in the % FVC changes observed.

Immunogenicity: The ELISA assay provided quantification of the antibody response by titers expressed as OD----units per µl of serum, but the assay was somewhat non-specific to laronidase, probably because of cross reactivity with a 60 kD protein impurity present in the final product. With the ELISA antibody assessments 5 placebo-treated subjects became seropositive while all laronidase-treated subjects became seropositive. The anti-laronidase antibody became detectable early in the study, between weeks 4 and 8. There was no correlation between the anti-laronidase IgG antibody levels, as determined by ELISA and the % FVC change from baseline at week 26.

Radioimmunoprecipitation (RIP) was used as a confirmatory assay for the ELISA, due to its specificity to laronidase as a substrate. The RIP is a qualitative assay only. Assessing immunogenicity with RIP, most laronidase-treated subjects (20/22) developed anti-laronidase antibodies. Only one placebo-treated subject had detectable anti-laronidase antibodies in only one timepoint, suggesting this was most likely a false positive or a mishandled serum specimen.

Reviewer's comment: In view of these data, comparisons between seropositive and seronegative laronidase-treated subjects regarding the change in % FVC were not informative.

Analysis by baseline enzyme level: There was no correlation between the baseline enzyme levels and the baseline %FVC or the change in % FVC at week 26 compared to baseline in the group as a whole or the 2 treatment groups.

Analysis by change in height: No discernible trends were seen in comparing the change in subjects heights during the 26 weeks of study with their change in FVC by treatment groups.

Six minute walk distance (meters)

Primary analysis

After 26 weeks of the study, subjects in the laronidase group had a median increase of 27.5 meters in the 6 minute walk distance, while subjects in the placebo group have shown a median decrease of 11.0 meters walked in the 6 minute interval. The overall difference, as analyzed by the Wilcoxon rank sum test, did not reach statistical significance between the treatment groups. Assessments for all subjects at baseline and week 26 were completed. Therefore no imputation for missing data was necessary. Table 17 shows the changes from baseline to week 26 in the 6 minute walk distance.

Table 17. Changes from Baseline (± SD) to Week 26 in median and mean 6 minute walk distance (in meters)

	Laronidase (n=22)	**Placebo (n=23)**	**p value**
Mean Baseline	319.1 ± 131.4	366.7 ± 113.7	
Mean Week 26	338.8 ± 127.1	348.3 ± 128.8	
Mean Change	19.7	- 18.4	
Mean Difference from Placebo	38.1		
Median Change	27.5	-11.0	0.07 *

*Wilcoxon test

Reviewer's comment: The trend was favorable to laronidase effect, but statistical significance was not reached. The clinical significance of this difference is also unclear. This endpoint was selected because the distance walked in the 6 minute walk test is an assessment of overall function, but probably indicates a measure of heart function, lung function, joint and neuromuscular function, all of these affected in subjects with MPS I, to a greater or smaller extent. The sponsor conducted a cross sectional survey (ALID-004) of subjects with MPS I in order to plan the Phase 3 study and the endpoints to be used in the pivotal study. The results of the 6 minute walk distance obtained from ALID-004 have shown that these subjects can walk longer distances than previously thought. Unlike % FVC, there was no effort to limit enrollment to subjects substantially affected in their capacity to walk, which may have limited the ability to observe a clinical effect and contributed to lack of statistical significance. However, a sensitivity analysis conducted post-hoc comparing the effect of laronidase treatment to placebo in subjects above and below the median for those groups failed to demonstrate an effect of the test drug in the most severely affected subjects. Please refer to this and other sensitivity analyses described below.

The 95% Confidence Interval for the between-groups difference in change from baseline to week 26 in the distance walked in 6 minutes is –2.0 – 79.0 meters.

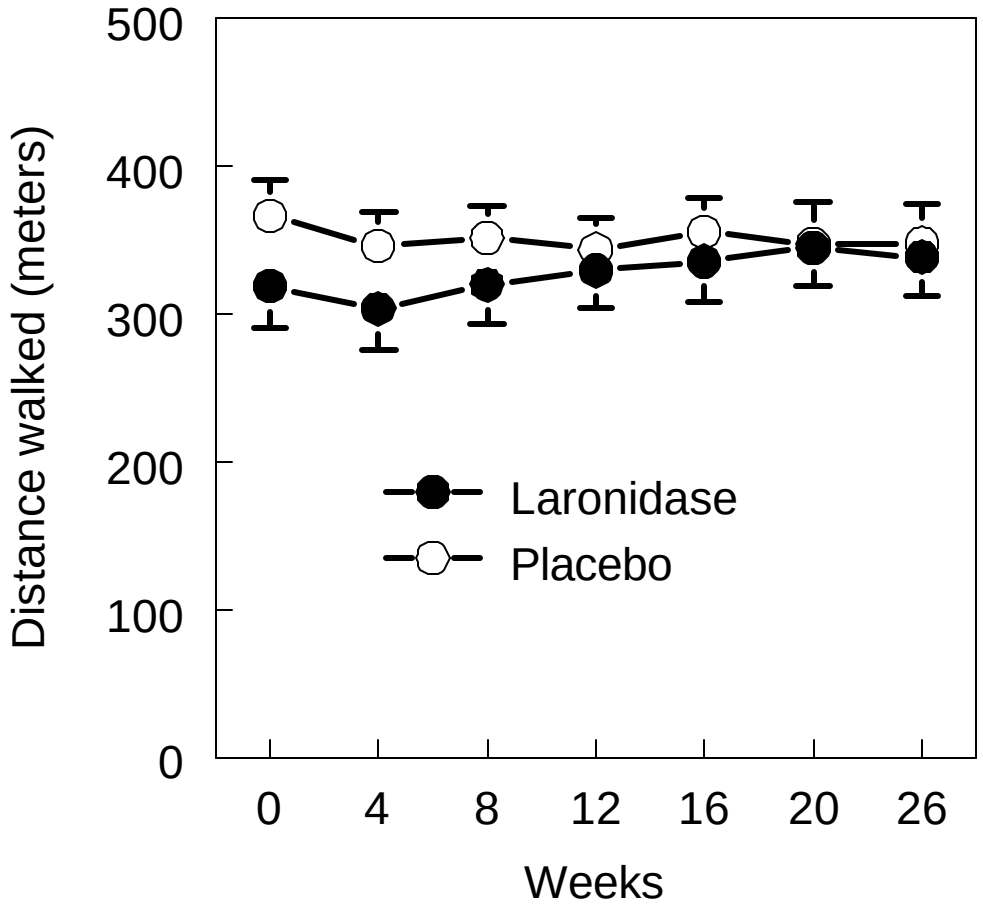
Exploratory Analysis

Prospectively Defined Exploratory Analysis

Analysis of covariance was performed with center, baseline 6 minute walk distance, gender, baseline standing height, and baseline liver volume used as covariates. In this model, the treatment effect p-value achieved statistical significance (p=0.04). This treatment effect was seen in the ANCOVA after controlling for the significant covariates of gender (p=0.02) and baseline 6 minute walk distance (p < 0.001).

Analysis by Study Visit: Figure 5 demonstrates the effect of laronidase treatment on the 6 minute walk distance across the study period, as compared to control.

Figure 5. Mean (± SD) distances walked across the 26 weeks of Study 003 by treatment group



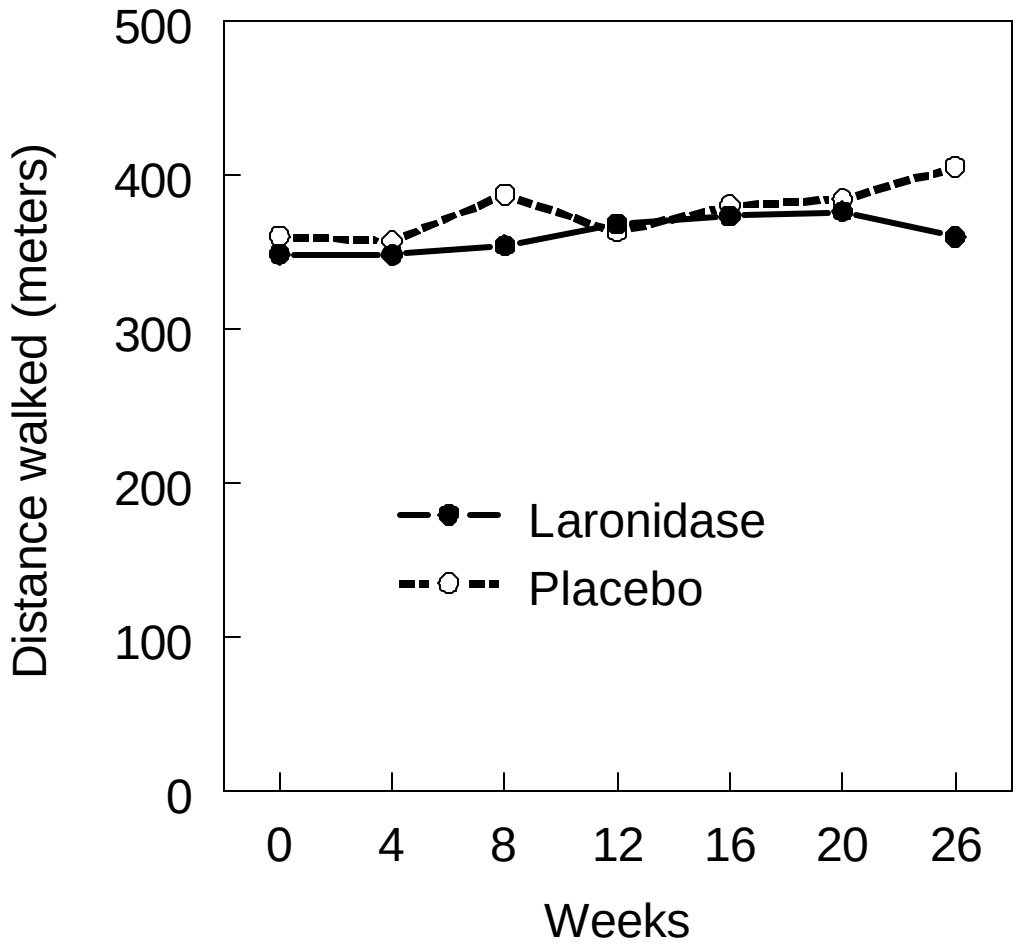
Reviewer's comments: The drop observed for both treatment groups between baseline and Week 4 is attributed to the training effect obtained by selecting the third measurement of this test in a period of approximately 7 days for determination of baseline. There is a small but consistent increment in distance between the first and the third of these initial assessments. The effect of training is likely lost after a 4 week interval. The same training effect was not observed in the analysis among the 3 baseline measures of % FVC for determination of the baseline value for that endpoint.

Another observation is related to the lower mean distance walked by the laronidase-treated group as compared to placebo. However, unlike the data shown for the % FVC, here there is small but consistent improvement in the distance walked in 6 minutes in the laronidase-treated group, even if with unclear clinical significance. Unlike the graphic

shown for the % FVC by study visit, the laronidase-treated group does not show a remarkable mean increase in the Week 20 to Week 26 interval.

Another analysis relevant in these non-parametric data is to plot the changes in the medians of distances observed for each treatment group by study visit (Figure 6)

Figure 6. Median distances walked in the across the 26 weeks of Study 003 by treatment group.



Reviewer's comment: It is interesting to note that, while the median distances walked by the laronidase group changes in 6MWD reproduce the mean distances for the group within the 26 weeks of Study 003, the plot of the median distances walked by the placebo group shows a large increase in distance at week 8 (30 meter) with a drop to near baseline, and again a large increase in distance at week 26 (21 meters). This figure shows an apparent benefit for the placebo, due to the brisk changes in group medians occurring among the study visits. Table 17, on the other hand, shows the median of the changes observed in both treatment groups from baseline to week 26. This emphasizes

that while mean change from baseline to week 26 is the same as the difference between the means at baseline and week 26, this is not true for analyses of the medians.

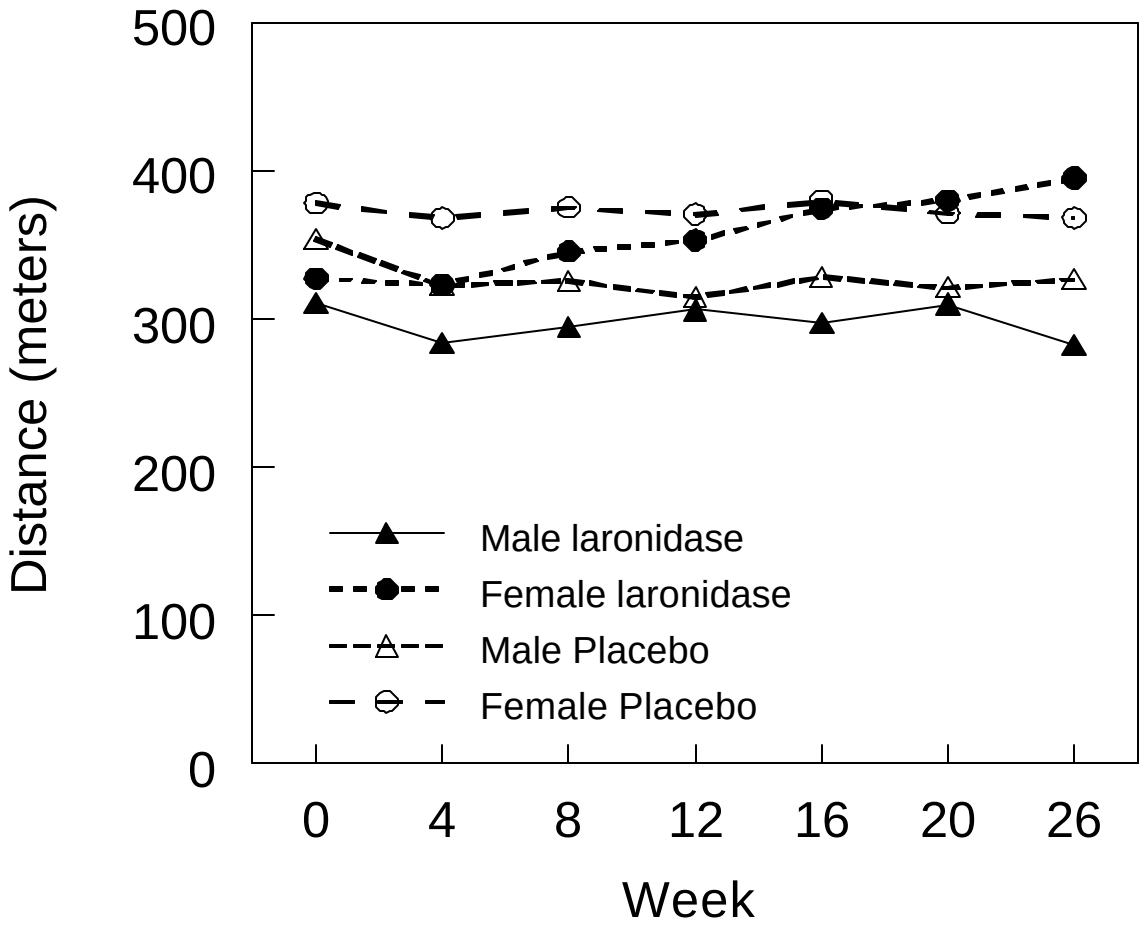
Analysis by Gender

Reviewer's comment: Further analysis into the covariates that drove the statistical significance in this ANCOVA has demonstrated that the favorable difference from placebo came from females, as shown in Table 18 and Figure 7. These findings are similar to those related to laronidase effects on % FVC by gender; where only laronidase-treated females showed improvement. Unlike the % FVC data, there was no difference in the change from baseline in distances walked by both male treatment groups.

Table 18. Baseline, Week 26 mean (± SD) distances walked and mean changes in the 6 minute walk distance from baseline to Week 26 by Gender

	Timepoint	**Laronidase**	**n**	**Placebo**	**n**
Female	**Baseline**	327.6 ± 107.7	11	378.1 ± 104.4	12
	Week 26	395.2 ± 82.8		368.1 ± 121.1	
	Change	67.5		- 10.0	
Male	**Baseline**	310.5 ± 157.0	11	354.2 ± 126.9	11
	Week 26	282.4 ± 141.6		326.7 ± 139.3	
	Change	- 28.1		-27.5	

Figure 7. Mean distance walked in 6 minutes across the study visits plotted by gender and treatment groups



Reviewer's comment: As seen in the % FVC figure by study visit and gender, the laronidase-treated males had a lower baseline distance compared to the other 3 groups. Both the figure and the table clearly show the contribution of the laronidase-treated females to the marginal treatment effect seen.

Analysis by Impairment: The prospectively planned analysis by impairment at baseline, dividing the treatment groups into a mild subset (distances walked above the aggregate group median of 358 meters) and a severe subset (distance walked below the group median) did not yield any significant differences in the pattern compared to the study overall (Table 19).

Table 19. Baseline and Week 26 mean (± SD) distance walked in the 6 minute walk test according to impairment at baseline

Severity	Placebo			Laronidase		
	n	Baseline	Week 26	n	Baseline	Week 26
= 358 meters	13	439.9 ± 67.0	425.0 ± 76.6	10	419.2 ± 69.7	439.4 ± 62.4
< 358 meters	10	271.4 ± 88.2	248.7 ± 115	12	235.6 ± 110.6	254.9 ± 103.7

Reviewer's comment: A more informative analysis of the mean changes in the 6 minute walk distance by degree of impairment could be done, as seen in Table 20, dividing the 45 participating subjects into 4 quartiles by mobility at baseline.

Table 20 . Mean changes (± SD) from baseline to week 26 in the 6 minute walk distance by the quartiles of impairment at baseline

Severity level	***Distance range***	***Laronidase***	***n***	***Placebo***	***n***
least ↓ *most*	*411 – 591*	*-5.3 ± 74.0*	*3*	*-19.6 ± 61.4*	*8*
	358 – 411	*31.1 ± 64.7*	*7*	*-7.7 ± 95.1*	*4*
	276.5 – 358	*-8.4 ± 60.9*	*5*	*-28.1 ± 83.6*	*7*
	14 – 276.5	*39.1 ± 80.1*	*7*	*-9.2 ± 33.1*	*4*

No trend related to impairment at baseline can be distinguished.

Post-hoc Exploratory Analysis

Some effect of the age categories contributed to differences between the treatment groups, as shown in Table 21.

Table 21. Baseline and Week 26 mean (± SD) 6 minute walk distances and difference between treatment groups in the changes by Age Category

Age category	Placebo			Laronidase		
	n	Baseline	Week 26	n	Baseline	Week 26
6 - 12	10	410.4 ± 119.3	382.9 ± 120.6	12	321.8 ± 121.0	353.6 ± 127.7
		Difference between groups: **59.3 meters**				
13 – 18	8	308.8 ± 112.9	274.6 ± 142.6	3	482.3 ± 111.6	480.7 ± 33.2
		Difference between groups: **32.5 meters**				
19 – 43	5	371.8 ± 72.3	397.0 ± 78.2	7	244.3 ± 97.8	252.6 ± 84.0
		Difference between groups: **- 16.9 meters**				

Reviewer's comment: The trend to greater treatment effect in the younger subset is consistent with what was observed with the % FVC efficacy endpoint. In addition, a comparison of the baseline data among the 2 treatment groups in the different age categories reveals more imbalances in these subsets than the imbalance observed at baseline for % FVC. Therefore a change in the absolute distance walked (in meters) between the 2 treatment groups, rather than the comparison of distance walked at week 26, is more readily interpretable. Although there are few subjects in the older age categories, these data suggest the possibility that intervention at an earlier age may be favorable, when reduction of accumulated GAG's in heart, lungs and joints become more resistant to therapy. On the other hand, the data suggest that treatment with laronidase may not be useful in older patients.

Analysis of subject distribution according to gender, age category, treatment assignment and impairment of 6 minute walked distance at baseline

As seen from the data on 6MWD changes in the 2 treatment groups by age category and gender, these demographic factors influenced the treatment effect on this primary endpoint. Table 14 (see above) has already shown that subjects in both genders were reasonably well distributed in the age categories used in the analysis. Therefore any effect of each of these demographic characteristics (age and gender) on the outcomes of the study can be separately identified. Table 22 and Table 23 show the distribution of subjects according to impairment of the distance walked in the 6MWD at baseline by gender and by age category respectively.

Table 22. Distribution of subjects by gender and mobility impairment in the 6MWD at baseline.

Gender	Impairment of 6MWD	Treatment (n)	
		Laronidase	Placebo
Female	411 – 591	1	5
	358 – 411	5	1
	276.5 – 358	3	4
	14 – 276.5	2	2
Male	411 – 591	2	3
	358 – 411	2	3
	276.5 – 358	2	3
	14 – 276.5	5	2

These data show that subjects in both genders were reasonably well distributed in the severity of baseline categories used in the analysis. Therefore any effect of each of these demographic characteristics (impairment of 6MWD at baseline and gender) on the outcomes of the study can be separately identified.

Table 23. Distribution of subjects by age categories and impairment of 6MWD at baseline.

Impairment of 6MWD	Age Category (years)	Treatment (n)	
		Laronidase	Placebo
411 – 591	6 - 12	1	5
	13 – 18	2	1
	19 - 43	0	2
358 – 411	6 - 12	6	2
	13 – 18	1	1
	19 - 43	0	1
276.5 – 358	6 - 12	2	2
	13 – 18	0	4
	19 - 43	3	1
14 – 276.5	6 - 12	3	1
	13 – 18	0	2
	19 - 43	4	1

Only 3 subjects who could walk above the median distance of 358 meters were older, while 8 older subjects were able to walk less than the median distance. Conversely, 14 subjects younger than 12 years walked above the median distance, whereas only 8 subjects in the same age category walked below the median distance for the whole group. Because older subjects and more severe disease are associated with the least effect of laronidase on the 6MWD, one cannot conclude that gender and baseline severity in 6MWD played separate roles in the limited laronidase effect in these subsets.

Analysis by Study Center: When laronidase treatment effect was analyzed among the 5 clinical sites a significant effect was found (p=0.03), with a 96.7 meters difference from placebo in the 6 minute distance walked at the University of North Carolina (3 subjects in each treatment group) contrasted with a – 14.3 meters difference in the New York site (4 placebo-treated and 3 laronidase-treated subjects). Overall, placebo treated subjects improved in 2 / 5 centers, whereas laronidase-treated subjects improved in 4 / 5 centers (Table 24). However, the numbers are very small for one to be able to drawn any conclusions from these data.

Table 24. Mean changes (± SD) from baseline to week 26 in 6 minute walk distance in Study ALID-003 by Clinical Site

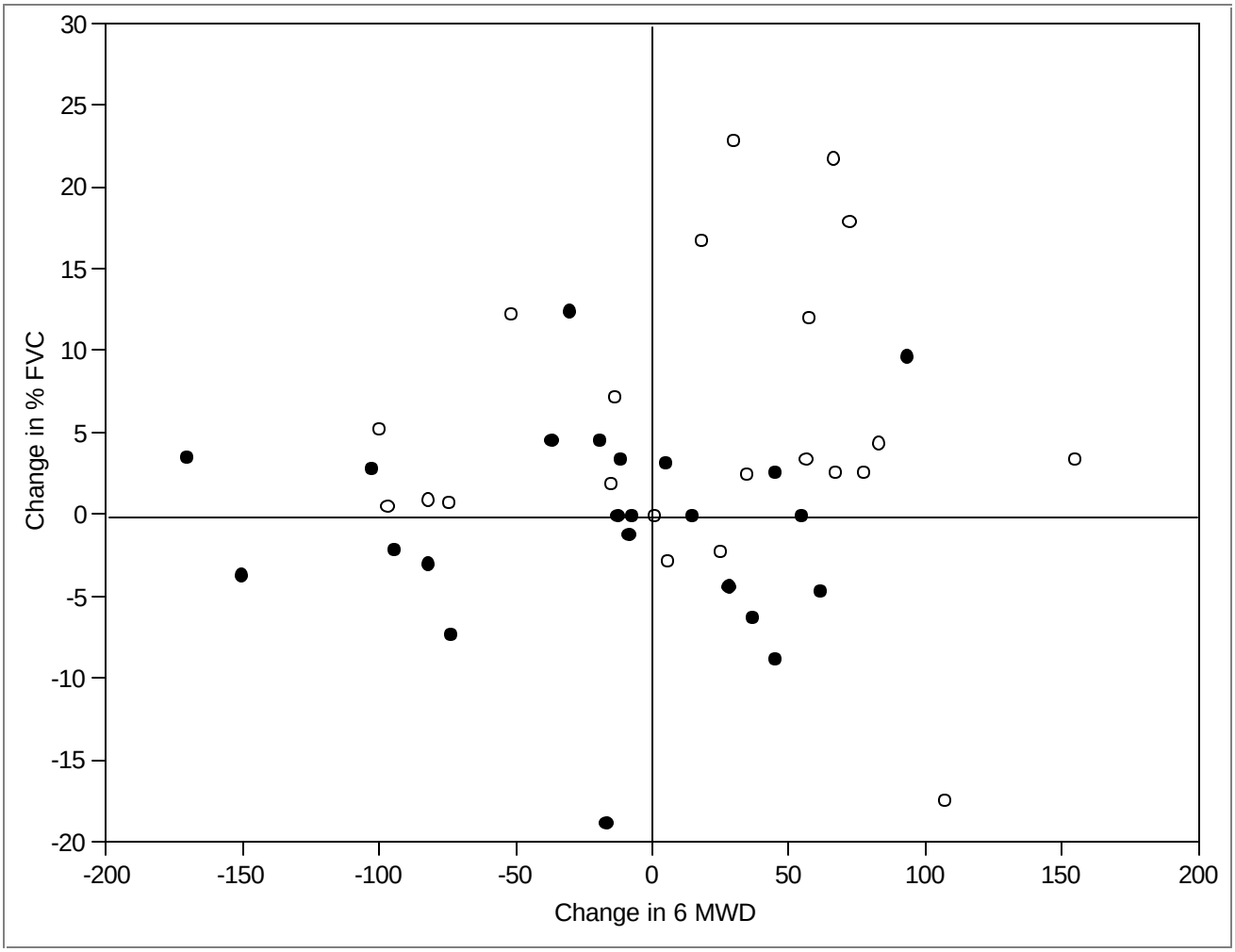
	Laronidase	n	Placebo	n
1. United Kingdom	9.5 ± 92.2	6	-54.5 ± 74.9	5
3. Germany	48.0 ± 68.7	4	9.8 ± 34.9	5
4. North Carolina	69.7 ± 10.41	3	-27.0 ± 105.8	3
5. New York	25.7 ± 51.4	3	40.0 ± 17.3	4
6. Canada	-16.8 ± 58.4	6	-44.6 ± 61.7	5

Analysis of effect of anti-laronidase antibodies: The anti-laronidase antibody became detectable, using the ELISA assay, between weeks 4 and 8 for most laronidase-treated subjects (20/22). Therefore, comparisons between seropositive and seronegative subjects regarding the change in the 6 minute walk distance were not informative. There was no correlation between anti-laronidase IgG antibody levels, as determined by ELISA and the 6 minute walk distance change from baseline at week 26.

Analysis by baseline enzyme level: There was no correlation between the baseline enzyme levels and the baseline 6 minute walk distance or the change in 6 minute walk distance at week 26 compared to baseline in the group as a whole or the 2 treatment groups.

Analysis by treatment effect in the change of % FVC from baseline: There is no correlation between the direction and magnitude of change from baseline to week 26 between the data observed for % FVC and for the 6 minute walk distance, as seen in Figure 8. Subjects who demonstrated improvement in one of the primary endpoints cannot be predicted to have demonstrated improvement in the other primary endpoint. The observed changes in % FVC in the laronidase-treated subjects are not large enough to prolong the distance walked in 6 minutes for these subjects.

Figure 8. Baseline to week 26 changes in the % FVC plotted against the changes in the 6 minute walk distance in Study 003 by treatment group in individual subjects



Legend: Points shown as filled circles represent placebo-treated subjects and points represented as empty circles represent laronidase-treated subjects.

Secondary endpoints

Apnea / Hypopnea Index (AHI) of the sleep study

Primary Analysis

The endpoint used for the analysis of efficacy was the mean AHI change from baseline to week 26 ANOVA comparison between the treatment groups. The AHI is defined as the number of apnea (cessation of airflow for 10 or more seconds) and hypopnea (50% decrease in airflow per breath accompanied by arousal or desaturation) events divided by the hours of sleep, reported as events per hour. Therefore a decrease in the index is a favorable event. The laronidase-treated subjects experienced an AHI decrease of 2.9, whereas the placebo-treated subjects had a 0.4 increase in the AHI. The difference from placebo of –3.6 events per hour was favorable to laronidase but did not reach statistical significance (p=0.14). The clinical significance of this finding is questionable.

Exploratory Analysis

The independent expert who performed the blinded readings of the sleep studies had noted that a significant number of subjects (18 / 21 placebo-treated and 11 / 20 rhIDU-treated) had normal AHI at baseline (< 20), which could have obscured the treatment effect in those with sleep apnea. He recommended an analysis of the results from subjects younger than 15 years with AHI scores = 10 and adults with AHI scores = 15, based on recently published guidelines (American Academy of Sleep Medicine Report: Sleep-Related Breathing Disorders in Adults: Recommendations for Syndrome Definition and Measurement Techniques in Clinical Research. *Sleep 1999, 22(5):667-689*. and American Academy of Pediatrics, Clinical Practice Guideline: Diagnosis and Management of Childhood Obstructive Sleep Apnea Syndrome. *Pediatrics 2002 Vol. 109(4):704-714*).

Table 25 shows the data and comparative analysis in the subjects with clinical sleep apnea/hypopnea at baseline.

Table 25. Baseline and Week 26 mean (± SD) changes in Apnea/Hypopnea Index (AHI) in Pediatric Subjects with baseline AHI = 10 and Adult Subjects with baseline AHI = 15

	Statistic	Laronidase (n=11)	Placebo (n=8)
More severe AHI	**Mean Baseline**	32.1 ± 18.7	26.8 ± 17.6
	Mean Week 26	25.8 ± 18.6	25.8 ± 17.2
	Mean Change	- 6.3	- 1.1
	Mean Difference	- 5.2	
Less severe AHI	**Statistic**	**Laronidase (n=9)**	**Placebo (n=11)**
	Mean Baseline	6.2 ± 2.7	6.2 ± 3.6
	Mean Week 26	7.6 ± 5.1	8.0 ± 6.8
	Mean Change	1.3	1.5
	Mean Difference	0.2	

Reviewer comment: There is a favorable trend in the decrease of the number of events during sleep studies among those subjects most severely affected by sleep apnea / hypopnea that were treated with laronidase during Study 003. However, this is a small exploratory subset analysis which does not permit reaching conclusions on the clinical or the statistical significance of these data. No difference could be detected between treatment groups in the AHI for the subjects with few apnea / hypopnea events.

BioMarin analyzed these subset data with adjusted mean changes using ANOVA with a change from baseline to week 26 in the placebo-treated group of 0.3 (n=8) and a change in the laronidase-treated group (n=11) of – 6.3, and a difference between groups of – 9.1 (p= 0.04)

The expert also recommended analyzing results from all subjects with AHI = 20, a criterion that may warrant nasal CPAP intervention when apnea-related symptoms are present. The

fact that only 3 subjects allocated to placebo had an AHI = 20 did not allow a meaningful between-groups subset analysis. However, the 9 laronidase-treated subjects who had AHI = 20 at baseline demonstrated a decrease of 7.4 events / hour. Among these laronidase-treated subjects 4 reduced the AHI from = 20 to < 20.

Reviewer's comment: It is clinically meaningful to make comparison among the subjects that are more severely affected, particularly the ones considered for medical intervention. However, no between-group analysis is possible so no conclusions can be drawn from this subset comparison.

Liver volume

Primary analysis

The endpoint used for the analysis of efficacy was the mean liver volume change from baseline to week 26 ANOVA comparison between the treatment groups. A statistically significant change occurred favoring the laronidase-treated group, with a mean 18.9 % decrease (n=22) as compared to a 1.3 % liver volume increase in the placebo-treated subjects (n=22) (p=0.001).

Prospectively Defined Exploratory Analysis

Of the 14 placebo-treated subjects with hepatomegaly at baseline, 3 subjects (21%) were considered to have reached normal liver volume at week 26. Of the 18 subjects with hepatomegaly at baseline in the laronidase-treated group, 13 (72%) had liver volume normalized by week 26.

All clinical sites had shown substantial reductions in liver volume for their laronidase-treated subjects, and only the University of North Carolina site had shown a reduction in liver volume among placebo-treated subjects.

Reviewer's comment: These results replicate the findings of the Phase 1 study, now in a randomized controlled trial. The findings provide strong evidence of bioactivity of the enzyme in that it facilitates the clearance of liver-accumulated heparan and dermatan sulfate. This could be considered a clinical marker of the activity in MPS I, but the role as a surrogate for clinically meaningful endpoints is not established. It is important to notice that liver function is normal in these individuals with hepatomegaly, and the main negative effect of hepatomegaly, if any, might relate to the volume burden in respiratory restriction and discomfort. On the other hand, GAG-related hepatomegaly in MPS I may carry no clinical implications. There is no correlation between the laronidase-treated subjects liver volume at baseline and the magnitude of reduction achieved during the 26 weeks of laronidase treatment.

Disability Index from the CHAQ or HAQ

Primary Analysis

The Disability Index was derived from the Children's Health Assessment Questionnaire (subjects aged 5 –18 years) and the Health Assessment Questionnaire (subjects aged 19 years and older) and is an overall summary score from 8 different categories that address dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities. The extent of disability is evaluated using a scale of 0 to 3, with 3 being the worst score. However, these assessment tools have not been validated in this disease.

The endpoint used for the analysis of efficacy was the mean change from baseline to week 26 ANOVA comparison of the Disability Index between the treatment groups. The mean Index for placebo subjects was 1.9 at baseline and 1.8 at week 26, whereas the mean score for laronidase-treated subjects was 2.0 at baseline and 1.9 at week 26. Neither group showed any changes from baseline using these tools.

Prospectively Defined Exploratory Analysis

Comparisons of subsets based on severity (above and below the baseline median value) were inconclusive. There were no significant variations on these findings among different study centers.

Shoulder Flexion

Primary analysis

The shoulder flexion variable for this analysis was defined as the mean of right and left shoulder flexion. The endpoint for the statistical comparison using ANOVA was the change in flexion degrees from baseline to week 26 between both treatment groups.

The difference between the groups was not statistically significant (p=0.99), with a mean decrease of 4.6 degrees in the placebo-treated subjects and a mean decrease of 1.2 degrees in laronidase-treated subjects.

Prospectively Defined Exploratory Analysis

Exclusion of 2 subjects (one placebo-treated and one laronidase-treated) with baseline cervical cord compression and large decreases in shoulder flexion did not change the overall between-groups difference. Analysis by severity (above and below the overall group median) at baseline yielded inconclusive results as well: a 4.9 degree mean change for the placebo-treated group and a – 0.7 degrees change in the laronidase-treated group for the subjects above the overall median, and a – 4.3 degrees and a 9.6 degrees for the placebo-treated and laronidase-treated groups, respectively for the subjects with baseline shoulder flexion below the median. The New York clinical site had results clearly different from the other sites, as the investigators observed a decrease in shoulder flexion of about 40 degrees in the placebo-treated group and about 60 degrees for the laronidase-treated group.

Reviewer's comment: It seems clear that the choice of shoulder flexion as a secondary endpoint is based on the findings from the Phase 1 study suggesting a larger change

from baseline for this joint in the 10 MPS I subjects treated with laronidase. The sponsor has not presented any rationale for this choice, as opposed to other joints range of motion assessments, nor is the shoulder more clinically significant than other joints studied in the Phase 1 trial. No conclusion can be drawn from these data on the effect of laronidase treatment in the shoulder flexion ROM.

Tertiary Endpoints

Urinary GAG levels (in µg / mg creatinine)

The endpoint for the statistical comparison using ANOVA was the mean % change in urinary GAG levels from baseline to week 26 between the treatment groups. The mean (± SD) urinary GAG levels increased from 183.3 ± 72.0 at baseline to 250.2 ± 105.1 at week 26 among the placebo-treated subjects, whereas the mean urinary GAG levels decreased from 188.9 ± 60.9 at baseline to 81.3 ± 26.4 at week 26 among the laronidase-treated subjects. The difference from placebo in mean % change from baseline to week 26 urinary GAG was 101 % ($p<0.001$). All laronidase-treated subjects had reductions of their urinary GAG levels, with substantial decreases seen as early as at week 4 and maintained through week 26. Despite the substantial reduction in the laronidase group, no subjects in that group reached the normal range for urinary GAG levels. These results were consistent across study centers.

Reviewer's comments: Studies in the canine model of MPS I revealed decreased vacuolation in glomerular mesangial cells and distal cortical tubules following treatment with laronidase as a histologic evidence of GAG clearance. However, patients with MPS I have no demonstrable impairment in renal function, and therapy with laronidase would therefore not be expected to favorably affect the kidney function. Therefore, reduction of urinary GAG levels can be seen as a marker of bioactivity, rather that demonstration of direct clinical benefit, similar to the interpretation of the reduction in liver volume.

Total Respiratory Events Index of the Sleep Study

The total respiratory event index is calculated from data generated in the baseline and week 26 sleep studies, as follows: number of apneas + number of hypopneas + respiratory effort-related arousals / hours of sleep. Mean changes from baseline to week 26 were compared in the treatment groups by ANOVA. Biomarin also assessed the total amount of sleep time spent with oxygen saturation below 90 % and below 80 % during the sleep studies. This index of hypoxemia was only descriptively summarized in the 2 treatment groups, and was not subject to hypothesis testing.

The laronidase-treated group showed a mean reduction of 3.1 events / hour, whereas the placebo-treated group had an increase of 0.3 events / hour at week 26. The difference from placebo did not reach statistical significance ($p=0.118$). These results were consistent across study centers. No clinical significance can be attributed to these data.

Pain Scales from the CHAQ / HAQ

The range of the pain scale is 0 to 3 with lower scores indicating less pain. The endpoint for the statistical comparison using ANOVA was the mean change in pain scores from baseline to week 26 between the treatment groups. The mean (± SD) baseline scores for the placebo-treated and laronidase-treated subjects were low and similar, at 1.0 (± 0.6) and 1.1 (± 0.89), respectively. Changes at week 26 for both groups were small, with scores of 0.8 ± 0.79 for placebo and 0.7 ± 0.87, and the difference in the adjusted mean changes from placebo was not statistically significant, using ANOVA (p=0.51).

Joint Range of Motion (ROM) Variables

After completing the final study report for ALID-003 on February 17, 2002, it was ascertained that the joint range of motion variables had been incorrectly assessed at several sites. To maintain the accuracy of the database, the joint range of motion measurements were corrected in the database. The tables, figures, and patient data listings that were affected by these changes were recreated. Where summary numbers cited in the study report text were affected, the report was updated. All changes were minor and did not change the interpretation of the study results.

Table 26 shows mean changes in joint ROM (angles) from baseline to week 26.

Joint		Laronidase	Placebo	p value
R Shoulder extension	**Baseline**	22.9 ± 13.3	28.9 ± 14.1	
	Week 26	27.7 ± 10.7	27.0 ± 8.6	
	Change	5.1	- 1.9	0.05
L Shoulder extension	**Baseline**	25.6 ± 10.6	28.0 ± 12.2	
	Week 26	27.7 ± 9.6	27.1 ± 6.9	
	Change	2.3	- 0.8	0.46
R Knee extension	**Baseline**	- 12.1 ± 13.4	- 14.3 ± 16.3	
	Week 26	- 9.0 ± 11.5	- 15.6 ± 16.7	
	Change	- 1.9	- 1.3	0.88
L Knee extension	**Baseline**	- 12.3 ± 13.8	- 15.4 ± 17.1	
	Week 26	- 9.6 ± 11.9	- 14.9 ± 16.6	
	Change	- 4.0	0.5	0.48
R knee flexion	**Baseline**	106.7 ± 19.9	114.4 ± 11.3	
	Week 26	115.1 ± 18.0	118.6 ± 12.3	
	Change	8.0	4.2	0.40
L knee flexion	**Baseline**	107.4 ± 20.3	117.0 ± 11.4	
	Week 26	116.6 ± 17.0	118.5 ± 15.7	
	Change	8.9	1.5	0.09

Higher values (in angles of flexion or extension) reflect less severe disease. For knee extension, the measures represent degrees of hyperflexion, and a more negative value reflects more severe disease. In the laronidase-treated subjects, modest improvements were observed after 26 weeks of study in the range of motion of all 6 joints, approaching statistical significance in right shoulder extension and left knee flexion changes compared to placebo control. These differences were slightly more pronounced in the comparisons among the more severely affected subjects (below the median aggregate value for each joint assessed). The findings were consistent across clinical sites, except for worsening of bilateral knee extension and flexion in the laronidase-treated subjects in the United Kingdom.

Reviewer comment: Biomarin did not present the range of motion for the joints studied in the subset of less affected individuals, so an impression on the absolute level of impairment at baseline cannot be formed. A conclusion on the clinical significance of the changes shown cannot be drawn.

Global Components of the Child Health Questionnaire (parent / caregiver and child subject components) or from the Short-Form 36 (SF-36)

There were multiple analyses performed on components of these tools. Most did not show statistically significant differences between groups. These analyses provide no support for efficacy of laronidase.

Height in pre-pubertal subjects

Only pre-pubertal subjects who had not reached Tanner Stage 2 by the end of week 26 were included in the analysis (7 subjects in each treatment group). Based on mean changes over the 26 week study period, the 7 laronidase-treated subjects grew 4.7 cm compared to 2.7 cm for the placebo-treated subset. The normal pre-pubertal height increase is approximately 5 cm per year. Many subjects had joint contractures at baseline, particularly at the knee. During the course of the study a slightly favorable trend in improved ROM of the knee in the laronidase-treated group was observed. The consequent release of these contractures may have accounted for some of the gains in height, more so in the laronidase group than in the placebo group. Therefore these data may not reflect linear growth, and no conclusions can be formed.

There were even fewer subjects with more than one historical standing height to be able to calculate pre-study slope values of growth velocity; therefore a clinically meaningful comparison of growth velocity was not possible between the treatment groups.

Shifts in Ophthalmology Measures, Visual Acuity and Tonometry

No conclusive data is derived from these assessments in the 2 treatment groups.

Cardiac Function based on EKG and echocardiography

Using standard EKG tracings, no clinically relevant changes in any parameters (heart rate, intervals, sinus rhythm, left or right ventricular hypertrophy, evidence of prior MI, non-specific ST wave abnormalities) were present in either treatment group.

No clinically relevant changes were seen in any of the echocardiographic parameters in either treatment group. Hypothesis testing failed to reveal any statistically significant changes in these parameters.

Investigator Global Assessment

This assessment is the investigator's global perception at week 26 as compared to baseline for each subject. Six of 22 laronidase subjects were considered as having marked or moderate improvement, whereas 2 of 23 placebo-treated subjects were considered by the investigators to have had the same improvement magnitude. 19 / 22 placebo-treated subjects and 13 / 22 laronidase-treated subjects were considered to have mild improvement or no change at week 26. Only one subject was designated as having marked worsening, laronidase-treated subject 30806, who had complications following heart valve surgery unrelated to the treatment group allocation. No benefits were apparent from these data.

Forced Expiratory Volume (FEV), Total Lung Capacity (TLC), and Diffusing Capacity (DL)

Baseline values for the 3 parameters were similar. Changes from baseline to week 26 were small and similar for both treatment groups.

Resource Utilization

Data on this endpoint was not included in the study report. The sponsor states: "Analyses of these data will be documented in a separate report."

Heart Rate, Respiratory Rate and Oxygen Saturation

Heart and respiratory rates, as well as O_2 saturation were determined before, immediately after and 2 minutes after the 6 minute walk distance test. No statistically or clinically meaningful differences were presented in these measurements between the treatment groups at baseline or at any of the timepoints for assessment, including week 26.

Composite endpoint

Biomarin created a post-hoc composite endpoint for a post-hoc exploratory analysis. The composite endpoint is based on changes in % FVC, 6MWD, AHI, shoulder flexion and liver volume. A responder to this composite endpoint is a subject who shows net improvements across the 5 domains. Using these exploratory criteria, 77 % of laronidase-treated subjects were responders and 17 % of placebo-treated subjects were responders. Even when the domain of hepatomegaly is removed from the composition of the endpoint the resulting analysis still shows 13 of 22 laronidase-treated subjects as responders, and 5 / 23 placebo-treated subjects as responders.

Reviewer comment: This post hoc analysis has several flaws that undermine a suggestion of clinical significance for the laronidase based on the data analyzed. It is an analysis conducted only after the data was unblinded, combining primary and secondary endpoints. It also implies that a net improvement in a specific domain is clinically significant (to be considered a response), which is unsubstantiated.

Pharmacokinetic Studies

All subjects randomized at the United Kingdom and the Canadian clinical sites participated in the pharmacokinetic studies. A total of 23 subjects (12 randomized to laronidase and 11 to placebo) took part and completed the study. Infusions at weeks 1, 12 and 26 were selected for the pharmacokinetic studies. Due to the short $t_{1/2}$ observed in the study relative to the weekly dosing frequency, each infusion was treated as a single dose for the purpose of pharmacokinetic analysis.

Table 27 shows selected pharmacokinetic parameters assessed in the 12 laronidase-treated subjects for Infusions 1, 12, and 26 representing the beginning, the middle and the end of the double blind period.

Table 27. Selected pharmacokinetic parameters associated with rhIDU infusions

Parameter	Infusion 1		Infusion 12		Infusion 26	
	n		n		n	
Dose (U/Kg)	12	105 ± 5	12	104 ± 3.3	12	103 ± 3.2
Infusion time (h)	12	3.98	12	4.00	12	3.96
C_{max} (U/mL)	12	0.197 ± 0.05	11	0.210 ± 0.08	12	0.302 ± 0.09
T_{max} (h)	12	3.93	11	3.83	12	3.92
AUC_8 (h·U/mL)	10	0.93 ± 0.21	6	0.91 ± 0.44	10	1.19 ± 0.45
CL (ml/min/kg)	10	1.96 ± 0.49	6	2.31 ± 1.13	10	1.68 ± 0.76
Vz (L/Kg)	10	0.60 ± 0.17	6	0.31 ± 0.14	10	0.24 ± 0.13
Vss (L/Kg)	10	0.44 ± 0.12	6	0.25 ± 0.08	10	0.22 ± 0.08
$?_z$ (h^{-1})	10	0.20 ± 0.05	6	0.77 ± 1.01	10	0.60 ± 0.52
$t_{1/2}$ (h)	10	3.61 ± 0.89	6	2.02 ± 1.26	10	1.94 ± 1.09
MRT (h)	10	3.84 ± 1.04	6	2.23 ± 1.21	10	2.36 ± 0.83

C_{max}=maximum plasma concentration; T_{max}= time to maximum plasma concentration; AUC_8=area under the plasma concentration – time curve to infinity; CL= total plasma clearance; Vz= mean volume of distribution; Vss= mean volume of distribution at steady state; $?_z$=terminal elimination rate constant; $t_{1/2}$=mean elimination half life; MRT=mean residence time.

Observations and conclusions derived from these studies:

- differences among the 3 infusions for C_{max}, Vz and Vss were statistically significant, using Friedman's test (p = 0.015)
- there was a trend toward an increase in C_{max} over the 26 week study
- CL does not appear to be affected by administration of rhIDU for 26 weeks
- there was a 50 % decrease in the Vz and Vss between Infusions 1 and 12 which remained constant until week 26
- therefore, increases in C_{max} were related to decreases in Vz
- decrease in Vz without changes in CL resulted in decrease in $t_{1/2}$ between Infusions 1 and 12, not statistically significant
- decrease in Vz may be related to antibody formation between Infusion 1 and subsequent pharmacokinetic studies. An inverse relationship between Vz and antibody levels was seen, causing the speculation that antibody-bound laronidase differs from unbound enzyme in its distribution, increasing the total body load in plasma and reducing the Vz
- following the infusion the plasma concentration of laronidase remained above the concentration for half-maximal saturation of uptake into cells, 0.7 nM (0.01 U /mL) for approximately 3 – 4 hours.

Reviewer's comment: CBER does not concur with the methodology used by BioMarin in the analysis of pharmacokinetic data. BioMarin has re-analyzed the data and will submit their results to FDA. Preliminary assessment based on BioMarin analysis show that

these findings were similar to those observed in canine studies, in which anti-laronidase antibodies resulted in decreased clearance and decreased tissue uptake of the enzyme. With a somewhat shorter half life after the first infusions, and a decrease of enzyme transfer to lysosomes in affected tissues (one could speculate as a consequence of antibody binding, even if not a neutralizing antibody in in vitro assays), a concentration to achieve half maximal saturation of uptake may be sufficient to result in biologic effects in certain organs and tissues, as seen in liver and kidney in this study, but not at other organs or tissues, such as central nervous system, heart, airways and joints. Data on half maximal saturation of uptake into cells is derived not from binding studies in histologic specimens but from fibroblasts in culture, possibly with different binding affinities.

Safety

AE's

The Safety population consists of the 45 subjects randomized to treatment, of which 22 received laronidase. AE's were recorded from the time of signing the consent form until 2 weeks after completion of the final study procedures. None of the subjects were discontinued from the study. 6 / 23 subjects in the placebo group and 10 / 22 subjects in the laronidase group had mild or moderate AE's during the baseline (pre-randomization) period. During the double blind period all placebo subjects and 21 / 22 laronidase subjects had = 1 AE's. Drug-related AE's were reported in 16 / 23 placebo subjects and in 12 / 22 laronidase subjects. Among the latter, infusion associated reactions (IAR's) occurred in 11 / 23 placebo subjects and in 7 of 22 laronidase-treated subjects. IAR's were defined as all drug-related AE's occurring on the day of infusion, except for those identified by protocol required assessments prior to the infusion.

All AE's with incidence higher than 30 % in either treatment group during the double-bind period were reported as organized by the World Health Organization Adverse Reaction terminology (WHO-ART) and identified by the Preferred Term. Headaches, fever and rhinitis were the most common AE's reported, and these were all more common in the placebo-treated group (Table 28).

Table 28. Summary of AE's with frequency = 30% during the double blind period

WHO-ART Body System	Preferred Term	Placebo		Laronidase	
		n	%	n	%
Central/Peripheral CNS Disorders	Headache	16	70	11	50
Body as Whole General Disorders	Fever	14	61	10	45
	Pain	7	30	5	23
Respiratory System Disorders	Rhinitis	10	43	8	36
	Coughing	6	26	7	32
	URTI	4	17	7	32
Skin and Appendages Disorders	Rash	5	22	8	36
Gastro-Intestinal System Disorders	Diarrhea	8	35	7	32
	Vomiting	9	39	5	23
Hearing and Vestibular Disorders	Earache	8	35	1	5

Of the less common AE's (those occurring in = 1 subject), arthropathy was present in 4 placebo- and 2 laronidase-treated subjects, back pain in 1 placebo- and 2 laronidase-treated subjects, and fever was reported in 3 placebo- and one laronidase subject. Two placebo subjects had diarrhea and abnormal gait, which none of the laronidase-treated subjects had.

AE's that were possibly, probably or definitely related to study treatment were reported more often in the placebo-treated group (16 / 23) than in the laronidase-treated group (12 / 22). From these, the most common were in the laronidase-treated group were flushing (5 / 22) and rash (3/ 22) whereas headache (6/ 23), flushing (4 / 23), arthropathy (4 / 23) and fever (3 / 23) were the most commonly reported study treatment – related AE's in the placebo group. The number of these study treatment related AE's was small, and the data showed no trend for any cluster of AE's in any body system associated with a specific treatment group.

Two placebo-treated subjects had severe AE's. Subject 50605 had worsening of the ankle flexion deformity, and subject 60809 had worsening of psoriatic lesions and increased hepatosplenomegaly. Six laronidase-treated subjects had severe AE's. Subject 30608 had worsening of otitis media, subject 60404 had worsening of arthropathy, subject 60908 had increased hepatosplenomegaly, and subjects 61010 and 61111 both had hepatomegaly. Laronidase-treated subjects 30806 and 40606 had severe AE's that are described below under SAE's.

Eleven of 23 placebo-treated subjects experienced 82 IAR's, whereas 7 / 22 laronidase-treated subjects had 66 IAR's. The most frequently reported IAR's in the placebo and laronidase treated groups were: flushing (4 / 23 and 5 / 22), fever (3 / 23 and 1 / 22),

headache (2 / 23 and 2 / 22) and rash (2 / 23 and 1/ 22) respectively. The majority of these IAR's were reported as mild. 5 / 23 placebo-treated subjects and 3 / 22 laronidase-treated subjects with IAR's required study drug infusion rate decrease or interruption, or medication with antipyretics and / or antihistamines.

The protocol called for IgE testing in subjects experiencing moderate or severe IAR's. 3 subjects with moderate IAR's were tested, being 2 in the laronidase group and one in the placebo group. The 3 tested negative for laronidase-specific IgE antibodies.

Data from AE's related to study drug occurring in non-infusion days was inconclusive.

Deaths and SAE's

There were no deaths during the study. One subject had a SAE during the baseline period of admission to the hospital due to worsening otitis media. She was later randomized to the laronidase-treated group.

During the double blind period, 3 laronidase-treated subjects had SAE's, as follows:

- Subject 10101, a 7 year old female with MPS I H-S, was admitted to the hospital with mild abdominal pain after the fourth infusion. She was diagnosed with constipation and treated with lactulose, with resolution of the AE and discharge from the hospital the following day.
- Subject 30806, a 43 year old male with MPS I S, had a past medical history significant for coronary artery disease, myocardial infarction in 1995, hypertrophic cardiomyopathy, dyspnea on exertion, and CPAP-requiring sleep apnea. On baseline examination he was found to have severe mitral and aortic stenosis and coronary artery disease. The subject complained of progressively worse chest pain and dyspnea and he informed the investigator at the 12^{th} infusion that he was unable to perform the 6 minute walk test due to severe dyspnea, chest pain and feeling of arrhythmia. The subject was admitted to the hospital, and severe aortic stenosis was demonstrated by echocardiogram. He underwent aortic valvuloplasty and mitral valve commissurotomy. The subject had a cardiac arrest due to ventricular tachycardia and fibrillation. Subsequently he developed pneumonia, sepsis, and renal failure. The subject was treated with antibiotics, hemodialysis and fully recovered, being discharged from the hospital 76 days after his admission. The subject had not received study drug infusion during his hospitalization, but resume infusions after his discharge.
- Subject 40606, a 7 year old female with MPS I H-S, complained of headaches and emesis, and was hospitalized for dehydration after completing 8 infusions. She was diagnosed with a partial obstruction of a ventricular shunt, and underwent a shunt revision. The subject made a recovery without sequelae, and was discharged the day following the procedure.

Clinical Laboratory Evaluations

There were few subjects in both treatment groups who had shifts from normal serum chemistry or hematology parameters at baseline to abnormal results at weeks 4, 12 or 26. Lactate dehydrogenase (LDH) and serum creatinine appeared to be the 2 parameters with most shifts from normal at baseline to abnormal, and these were balanced in the 2

treatment groups (4 subjects with LDH in each group, and 3 laronidase and 4 placebo subjects with serum creatinine shifts to abnormal).

One subject randomized to laronidase had a clinically relevant hematologic abnormality which, per protocol, was considered an AE: subject 60404 had a baseline platelet count of 210,000 / µl and at week 4 108,000 / µl. The platelet count normalized at Visits 12 and 26. The mean ± SD platelet counts in the laronidase-treated group increased from 218 ± 52 X 10^3/µL to 253 ± 72 10^3/µL (n=22), whereas in the placebo-treated group the platelet count decreased from 236 ± 66 X 10^3/µL at baseline to 212 ± 47 X 10^3/µL (n=21) at week 26.

No relevant changes in urinalysis were noted in either treatment group.

Vitals signs and physical findings

The vital signs assessed at baseline and just prior to the start and immediately after every infusion were systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature. The only variable that has shown a modest difference was the heart rate. A mild mean increase was seen in the laronidase-treated group and a mild decrease in the placebo-treated group, both in comparison to baseline as well as in comparison to pre-infusion heart rate.

Data available on changes in physical examinations compared to the baseline exam do not demonstrate any trends.

Other findings

No clinically significant electro- or echocardiographic changes from baseline were seen in either treatment group.

All subjects underwent brain and cranio-cervical junction MRI at baseline. All subjects were found to have abnormal findings in the MRI. The protocol called for a repeat MRI at the end of the study at the investigator's discretion. 9 placebo-treated subjects and 6 laronidase-treated subjects had a repeat MRI at week 26. From these, the MRI evaluations of the placebo-treated subjects remained unchanged, while the 1 /6 laronidase-treated subjects had a shift to a normal MRI at Week 26.

Screening for rhIDU IgG antibodies was performed with ELISA and confirmed with a radioimmunoprecipitation (RIP) assay. All laronidase-treated subjects and 5 placebo-treated subjects had detectable IgG titers by ELISA. The RIP assay confirmed the presence of anti-laronidase specific IgG in 20 / 22 laronidase-treated subjects and in 1 / 23 placebo-treated subjects. The latter tested positive only at a single mid-study timepoint, which the sponsor interpreted as a compromised sample. Given the large proportion of antibody formation in the laronidase-treated group, any correlation between serum anti-laronidase IgG antibodies and adverse events cannot be evaluated in a meaningful way. The effect of these antibodies on the 2 primary efficacy endpoints, in a qualitative analysis (i.e. presence or absence of antibodies) was equally inconclusive.

Reviewer's comment: An attempt to analyze levels of IgG antibodies as measured in OD units from the RIP assay with the primary efficacy outcomes across the 26 weeks of the study among laronidase-treated subjects failed to demonstrate a significant correlation.

Complement testing was performed in 3 subjects with moderate IAR's (1 placebo-treated and 2 laronidase-treated subjects) within one hour of the onset of the IAR. All 3 subjects had negative complement activation testing.

Summary

Study ALID-003 was able to demonstrate a statistically significant change in the % FVC for the overall laronidase-treated group compared to placebo, over the 26 weeks of the study. The data, however, does not demonstrate evidence of a progressive improvement in this endpoint seen through the 26 weeks of the study or for the laronidase-treated group as a whole. Rather, the benefit is shown by an abrupt improvement from week 20 to week 26 in the laronidase group, and an abrupt decrease in % FVC in the placebo group. The effect is also driven by an improvement seen in laronidase-treated females and in the younger subjects. The clinical significance of the increase in % FVC over the study period is marginal, with an absolute mean increase in FVC of 110 mL in the laronidase-treated group, compared to a 20 mL decrease in the placebo group.

The study has not shown a statistically significant difference in the other primary endpoint, the 6 minute walk test. Similar to the findings of subset analyses for the % FVC, a favorable trend is seen, mostly in females and the younger subjects in the laronidase-treated group.

The significance of these findings is unclear, but support to a claim of efficacy for all patients with MPS I is weak in this study alone.

This study suggests the possibility that younger and / or patients with less advanced disease may have some benefits from laronidase treatment, but this is not conclusively proven. Furthermore, older or subjects with more advanced disease have little evidence of benefit. The gender difference, with the observed better outcome for both co-primary endpoints in females, cannot be explained with physiologic arguments. Females in clinical trials show greater degree of compliance with the treatment and adherence to study visits, but the data in this particular study does not show greater adherence to the visit schedule by females, and the treatment is administered during the study visit, decreasing the role of compliance as a factor for differential success.

Study ALID-006

"A Multicenter, Multinational, Open-Label Extension Study of the Safety and efficacy of recombinant Human Alpha- L-Iduronidase in Patients with Mucopolysaccharidosis I".

Overview

This study is being conducted under IND 7334, according to protocol ALID-006-01. This is an open label extension of the double blind study ALID-003 reported above. It is an ongoing multicenter, multinational study of the same MPS I subjects who participated in the double blind, placebo controlled trial, which ended on September 6, 2001. The study period is planned to span 72 weeks or until market approval of laronidase. The study report covered in this review includes 24 weeks of data on this open label extension study, except for the 2 co-primary endpoints. BioMarin has submitted an amendment with an additional timepoint at week 36 during this ongoing Study 006. This review summarizes the results of the 6 MWD and the % predicted FVC from entry into study 006 until week 36.

This study has been conducted to provide additional long term safety and efficacy information on the use of laronidase in subjects with MPS I.

Protocol

1. **Title:** "A Multicenter, Multinational, Open-Label Extension Study of the Safety and efficacy of recombinant Human Alpha- L-Iduronidase in Patients with Mucopolysaccharidosis I". Protocol ALID-006-01. The original protocol was submitted on April 6, 2001

Design

This was a multicenter, multinational open label extension study of subjects with MPS I who had previously participated in the Study ALID-003 (double-blind 26 week study), for either 72 weeks or until laronidase obtains marketing approval.

All subjects previously allocated to placebo treatment under ALID-003 were treated with laronidase for this study. The 5 Centers that participated in Study ALID 003 continued to treat and follow subjects for all clinical evaluations. However the weekly infusions of laronidase and safety evaluations could be performed at one of 13 regional investigational sites closer to the subjects homes. The principal investigator for the 5 major sites would still be responsible for the full evaluation of the subject's medical condition and for all relevant safety issues, along with the Sponsor Medical Monitor.

Objectives

The objective is collection of additional long-term safety data and clinical effects of uncontrolled laronidase treatment. The interim study report described here includes safety and efficacy data for the first 24 weeks of this ongoing study.

Patients

Inclusion criteria:

- Must have signed new consent form for Study ALID-006

- Must have completed Study ALID-003 and have received at least 21 of the 26 consecutive weekly infusions under that study
- No safety issues that contraindicate participating in this study
- Females of childbearing potential must have a negative pregnancy test at study entry and use adequate contraception during the study.
- Sexually mature male subjects are advised to use a medically acceptable method of contraception during the study

Exclusion criteria:

- Pregnancy or lactation
- Use of investigational drugs other than those used in Study ALID-003 within 30 days prior to study enrollment
- Medical condition, serious intercurrent illness or other circumstances affecting compliance with laronidase treatment and study evaluations and follow ups.

Treatment assignment / Randomization

In this non-randomized study all eligible subjects were assigned to active treatment (laronidase).

Product Information and Administration

All subjects received laronidase at a dose of 100 U / kg intravenously weekly. For administration to subjects, the laronidase was diluted with between 100 mL to 250 mL of 0.1% human serum albumin in saline through week 24. Infusions of laronidase after week 24 were prepared without human serum albumin.

For details on the infusions and pre-treatment, please refer to 10. Study ALID-003, B. Protocol, 6. Product information and administration on page 34 of this review.

Amendment 1 was submitted on February 25, 2002 to remove the 0.1 % human serum albumin from the product formulation after week 24 of each subjects participation, due to potential safety concerns related to use of a human derived product. This formulation change is supported by a 26 week toxicity study in monkeys (in which there were no anaphylactoid reactions and one case of facial edema), and in normal dogs.

Evaluations

a. Forced Vital Capacity (FVC), reported as percent of predicted value based on standing height, at baseline (last measurement prior to randomization into Study ALID-003), at study entry (last measurement in Study ALID-003) and at Weeks 12, 24, 36, 48, 60 and 72.

- Six-minute walk distance, reported in meters walked, at baseline (last measurement prior to randomization into Study ALID-003), at study entry (last measurement in Study ALID-003) and at Weeks 12, 24, 36, 48, and 72. Heart rate, respiratory rate, and oxygen saturation will be measured prior to start, immediately following, and 2 minutes following the completion of the six-minute walk.

- Children's Health Assessment Questionnaire (CHAQ) for subjects 5 –18 years of age or Health Assessment Questionnaire (HAQ) for subjects 19 years of age or older are assessed at baseline (last measurement prior to randomization into Study ALID-003), at study entry (last measurement in Study ALID-003) and at Weeks 12, 24, 36, 48, and 72.
- Sleep study (to measure apnea/ hypopnea events and oxygen desaturation) are assessed at baseline (last measurement prior to randomization into Study ALID-003), at study entry (last measurement in Study ALID-003) and at Weeks 24 and 72.
- Liver volume by MRI at baseline (last measurement prior to randomization into Study ALID-003), at study entry (last measurement in Study ALID-003) and at Weeks 24 and 72.
- Urinary Glycosaminoglycans (GAG) at baseline (last measurement prior to randomization into Study ALID-003), at study entry (last measurement in Study ALID-003) and at Weeks 12, 24, 36, 48, 60 and 72.
- Joint Range of Motion at baseline (last measurement prior to randomization into Study ALID-003), at study entry (last measurement in Study ALID-003) and at Weeks 12, 24, 36, 48, 60 and 72.
- Child Health Questionnaire or SF-36 at baseline (last measurement prior to randomization into Study ALID-003), at study entry (last measurement in Study ALID-003) and at Weeks 24, 48 and 72.
- Resource utilization (event-based hospital data, home health care, therapist visits, MPS I medications, and related medical equipment, outpatient consultations, time lost from work or school activities due to MPS I for patients and caregivers) at baseline and at weeks 24, 48 and 72.
- Standing heights for measurement of growth velocity at baseline (last measurement prior to randomization into Study ALID-003), at study entry (last measurement in Study ALID-003) and at Weeks 12, 24, 36, 48, 60 and 72.
- Visual acuity by standard eye chart testing, ocular pressure, corneal clouding, and retina / optic nerve exam at baseline (last measurement prior to randomization into Study ALID-003), at study entry (last measurement in Study ALID-003) and at Weeks 24 and 72.
- EKG and echocardiogram at baseline (last measurement prior to randomization into Study ALID-003), at study entry (last measurement in Study ALID-003) and at Weeks 24, 48, and 72.
- FEV_1, total lung capacity and diffusing capacity at baseline (last measurement prior to randomization into Study ALID-003), at study entry (last measurement in Study ALID-003) and at Weeks 12, 24, 36, 48, 60 and 72.
- Medical history, VS, and physical examination, at baseline (last measurement prior to randomization into Study ALID-003), at study entry (last measurement in Study ALID-003) and at Weeks 4, 12, 24, 36, 48, 60 and 72.
- Laboratory evaluations at baseline (last measurement prior to randomization into Study ALID-003), at study entry (last measurement in Study ALID-003) and at Weeks 4, 12, 24,

36, 48, 60 and 72, including clinical chemistry, hematology and urinalysis. Urine pregnancy test for females of childbearing potential at baseline and every 4 weeks.

- Antibody testing at baseline (last measurement prior to randomization into Study ALID-003), at study entry (last measurement in Study ALID-003) and at Weeks 4, 8, 12, 16, 20, 24, 36, 48, 60 and 72. IgE and complement activation (CH100 or CH50 and C3 or C4 components) were measured if symptoms of a moderate or severe infusion associated reaction are noted.
- Adverse events

Safety Monitoring

An independent Allergic Reaction Review Board (ARRB) was created to review signs of moderate or severe hypersensitivity and provide guidance on management of these reactions. The ARRB interacted with the Genzyme Pharmacovigilance group and infrequently directly with investigators.

Endpoints

- Primary:

a. Percent predicted FVC: Mean change from baseline and from study entry to various timepoints in the study

b. 6 minute walk: Mean absolute change from baseline and from study entry to various timepoints in the study

- Secondary:

a. Sleep study – Apnea Hypopnea Index: change from baseline and from study entry to various timepoints in the study

b. Liver volume: % change from baseline and from study entry to various timepoints in the study

c. Shoulder flexion: change from baseline and from study entry to various timepoints in the study

d. Disability Index: change from baseline and from study entry to various timepoints in the study (derived from the Children's Health Assessment Questionnaire [CHAQ] / Health Assessment Questionnaire [HAQ])

- Tertiary:

a. Urinary GAG's

b. Total respiratory event index and total sleep time O_2 saturation less than 90 % and less than 80 % (derived from the sleep study)

c. Pain scale (derived from the Children's Health Assessment Questionnaire [CHAQ] / Health Assessment Questionnaire [HAQ])

d. Joint Range of Motion

e. QoL (derived from Child Health Questionnaire given to children 5 to 18 years old or the Short Form – 36 given to adult subjects)

f. Growth Velocity for pre-pubertal subjects

g. Visual Acuity, Ophthalmologic exam, tonometry, fundoscopy and slit lamp exam: shifts in normal / abnormal from baseline and entry to weeks 24 and 72

h. Cardiac Function Testing by electrocardiogram and echocardiogram parameters

i. Forced Expiratory Volume in One second (FEV1)

j. Total Lung Capacity

k. Diffusing Capacity

l. Heart rate, respiratory rate and O_2 saturation

Statistical Analysis

The ITT population was used for data analysis. The 2 treatment groups represented in the report are:

- laronidase / laronidase group which received laronidase infusions for 26 weeks in Study ALID-003 followed by laronidase infusions for 24 weeks in the present study
- placebo / laronidase group which received placebo infusions for 26 weeks in Study ALID-003 followed by laronidase infusions for 24 weeks in the present study

Missing data from missed study visits or early study dropouts were imputed with the LOCF method in the primary analysis, except for safety data, which were not imputed.

Demographic and baseline characteristics are summarized with frequencies and percentages for categorical variables and descriptive statistics for continuous variables.

Primary efficacy endpoints (% FVC and 6 minute walk distance) were analyzed by within group t test in the ITT population. Secondary analyses include the descriptive changes stratified by center, age, gender, seroconversion status and baseline severity.

Secondary endpoints were analyzed by the descriptive changes, without hypothesis testing. Additional analysis of the sleep study – AHI endpoint was performed in those subjects with AHI = 20 at baseline and for pediatric subjects with AHI = 10 or adult subjects with AHI = 15 at baseline. Liver volume changes were also reported in terms of shifts in normal / abnormal rates. The disability index and shoulder flexion were also reported on the basis of baseline severity.

Tertiary endpoints were analyzed by descriptive changes.

Study Conduct

Database Integrity

All CRF's were reviewed at the study site for completeness by a Genzyme Corporation clinical monitor. Genzyme conducted the data management and analysis. All data captured electronically (such as clinical laboratory data) was transferred electronically to the database. Upon completion of data entry the database receives a quality assurance check to ensure acceptable accuracy and completeness.

Genzyme Corporation was responsible for all data entry and editing and the statistical analysis and generation of the study report. All data editing was complete and decisions regarding subject data evaluability for inclusion in the statistical analysis was made prior to taking the snapshot for the entire 24 week study database.

Protocol Violations

Subject 30309 in the placebo/laronidase group had a heart transplant, violating exclusion criteria; Subject 30806 in the laronidase/laronidase group violated inclusion criteria by failing to receive at least 21 of the 26 infusions in the double blind study.

FDA site inspection findings

The findings of site inspections are pending at the time of writing this review.

Results

Subject disposition

The study started on May 29, 2001 and is still ongoing. The same 23 subjects allocated to the placebo treatment arm and the 22 subjects allocated to laronidase treatment are participating in Study ALID-006. The only treatment all subjects received was laronidase at a dose of 100 U / kg IV weekly. The 2 groups referred to in this study report are: laronidase / laronidase and placebo / laronidase, for the subjects continuing to receive weekly infusions of laronidase and for those switched to laronidase, respectively.

Study entry characteristics

Study entry characteristics are defined as the variables present at the time of the last infusion in the double blind study ALID-003. At study entry, the primary endpoint variables were distributed in the 2 treatment groups as shown in the Table 29

Table 29. Entry characteristics (mean ± SD) of primary endpoints in the treatment groups

Entry Characteristics	Placebo/laronidase n = 23	Laronidase/laronidase n = 22
Mean % Predicted FVC	53.6 ± 14.2	53.7 ± 18.6
Mean 6 min. walk distance (m)	348.3 ± 128.9	338.8 ± 127.1

Study drug exposure

The mean number of infusions in the placebo/laronidase treatment group was 21.6 and in the laronidase/laronidase group was 21.8, out of a maximum of 24 infusions reported in the

original BLA submission. The mean number of days in the study was 157.5 days in the placebo/laronidase group and 158.9 days in the laronidase/laronidase group. Subjects 10303, 60809, 30705 and 30806 missed 7, 9, 7 and 8 infusions, respectively. Study drug exposure was not reported in the BLA supplement updating the primary endpoints to 36 weeks.

Primary endpoints

Note: For the purpose of the review of this study report and to keep nomenclature consistent with the sponsor's designations, baseline is defined as the last measurement prior to randomization in the Study ALID-003 (Phase 3 double blind study) and study entry is defined as the last measurement obtained in study ALID-003.

Percent Predicted Forced Vital Capacity (% FVC)

Primary Analysis

From entry to week 36 the mean change in % FVC for the laronidase/laronidase group was a 0.5 % increase. The placebo/laronidase group had a 2.6 % increase in % FVC from study entry to week 36.
Table 30 shows the mean (± SD) changes in % FVC from baseline to week 36.

Table 30. Mean (± SD) changes in % FVC from baseline to week 36

	Laronidase/laronidase (n=22)	Placebo/laronidase (n=23)
Baseline	48.4 ± 14.8	54.2 ± 16.0
Entry	53.3 ± 18.5	53.5 ± 14.1
Week 36	53.8 ± 18.8	56.1 ± 16.0
Change from baseline to week 26 of Study 003	4.9	- 0.7
Change from entry into Study 006 to week 36	0.5	2.6

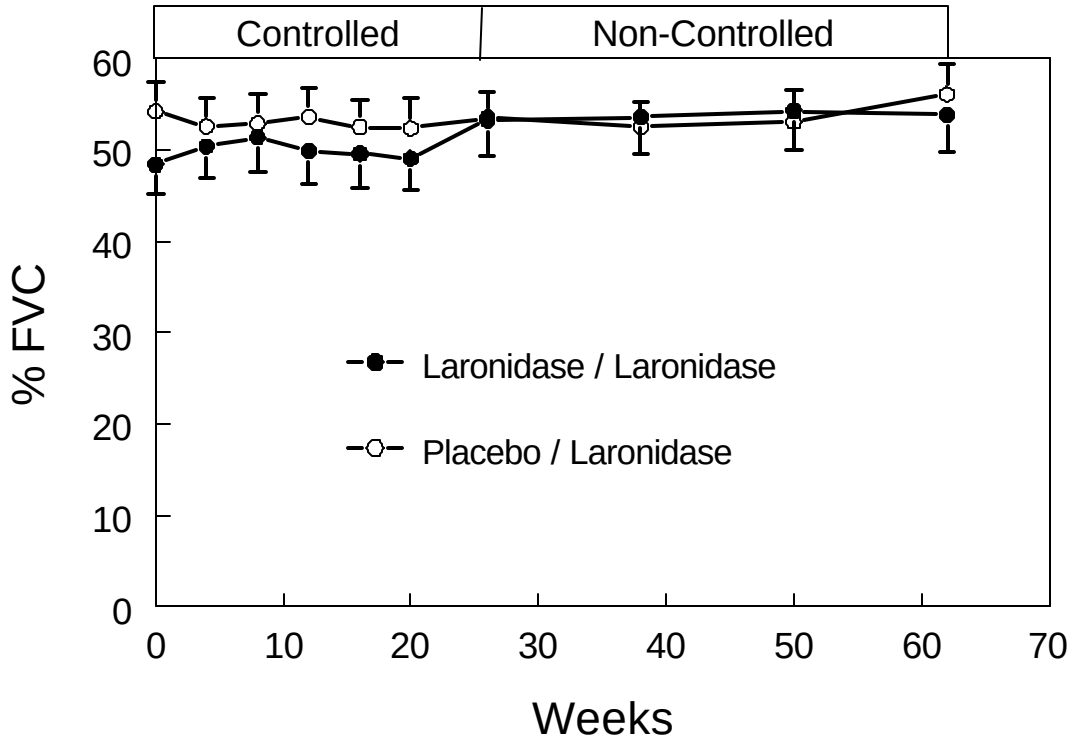
Reviewer's comment: The data on % FVC were calculated based on baseline height (height of the subjects upon entering study 003). The appropriateness of this calculation decreases in this study as compared to Study 003, as growth is expected to occur in both treatment groups after more than 1 year into the trial. Furthermore, the clinical significance of changes in % of predicted FVC, as calculated based on baseline heights, is unclear.
The response in both treatment groups is notable given the relatively favorable results observed for this endpoint in the double blind controlled study. After an initial improvement in the mean % FVC for the laronidase-treated group in 26 weeks of study, only an additional 0.6 % was obtained after another 24 weeks with the same treatment.

Even more significant is the fact that subjects initially exposed to placebo after receiving a 36 week laronidase treatment had their % FVC increased by only half of the increase seen in 26 weeks of laronidase treatment in Study 003. The sponsor attempts to make a justification of these data based on the fact that the placebo group had less severe restriction at baseline, or that missed infusions and seasonal changes contributed to these findings. However Study 003 suggests that subjects with less severe lung restrictions stand a better chance of improvement under treatment with laronidase, which is contrary to the argument used in the sponsor's interpretation of Study 006 data. Furthermore, there are no data to support the statement that seasonal changes or missed infusions in the placebo group contributed to the smaller magnitude of change of % FVC over the 36 weeks of laronidase treatment in the placebo-laronidase group.

Exploratory Analysis

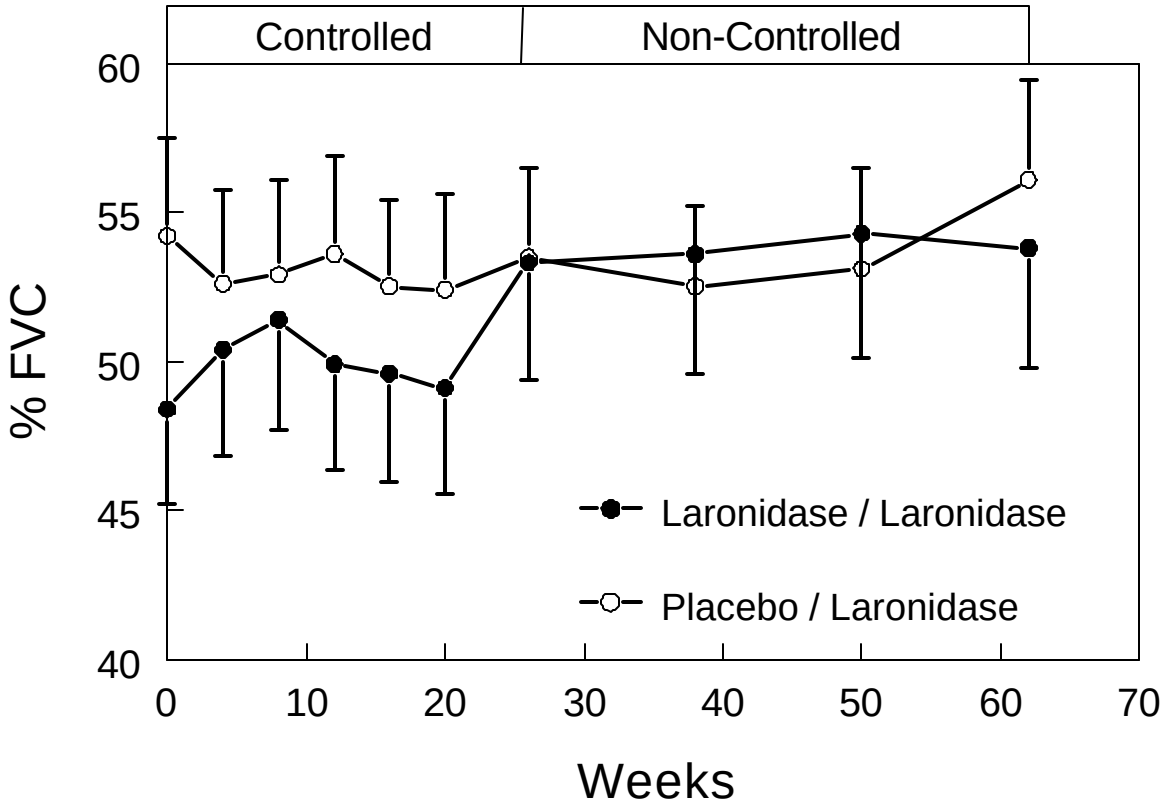
Analysis by Study Visit: Figure 9 shows changes in % FVC from baseline (calculated based on current height at the time of the study visits when the endpoint was assessed) through week 26 in the double blind study ALID-003 and through week 24 of the extension study ALID-006.

Figure 9. % FVC (calculated based on current heights) changes from baseline through 24 weeks in Study ALID-006.



Reviewer's comment: Because the 2 lines seem almost superimposed, the figure was amplified in the range 40 to 60 % where the subtle changes in predicted FVC were observed (Figure 10)

Figure 10. Mean (± SD) changes in % FVC from baseline through 36 weeks in Study 006, plotted in the range that changes occurred.



Reviewer's comment: This figure shows the small % FVC increase occurring in the placebo-laronidase group between weeks 24 and 36 of the Extension Study 006, while the laronidase-laronidase group has demonstrated no change in the % FVC during the 36 weeks of Study 006.

Analysis by Study Center: No significant differences were observed across different clinical sites. Table 31 shows the mean changes in % FVC for each site.

Table 31. Mean changes (± SD) from entry to week 36 in % FVC in Study ALID-006 by Clinical Site

	Laronidase/laronidase	n	Placebo/laronidase	n
1. United Kingdom	-0.3 ± 5.4	6	3.3 ± 3.2	6
3. Germany	4.0 ± 15.6	4	2.9 ± 6.7	5
4. North Carolina	-2.6 ± 1.1	3	2.9 ± 2.9	3
5. New York	-3.8 ± 8.4	3	5.3 ± 11.1	4
6. Canada	1.5 ± 9.4	6	-1.6 ± 4.8	5

Analysis by Gender: Table 32 shows the mean changes in each site for males and females in both treatment groups

Table 32. Mean changes (± SD) from entry to week 36 in % FVC in Study ALID-006 by Gender

Gender	Laronidase/laronidase	n	Placebo/laronidase	n
Females	1.1 ± 10.8	11	1.3 ± 4.7	12
Males	- 0.1 ± 6.5	11	3.9 ± 7.8	11

Reviewer's comment: These changes are relatively small and no apparent trends are evident from these numbers. While laronidase-treated females in the double blind study exhibited the largest improvement, no additional improvement was observed during the additional 36 weeks of laronidase treatment in females. Placebo-treated females in the double blind study did not realize the same apparent benefit in % FVC when they converted to laronidase treatment in the extension study. Males in the laronidase/laronidase were unchanged in their % FVC during Study 006. However, the males that converted from placebo to laronidase during Study 006 had the most % FVC increase, in contrast to the gender effects noted in Study 003.

Analysis by Age group: Table 33 shows the mean changes by age category in the % FVC from study entry to week 36 of Study ALID-006

Table 33. Mean changes (± SD) from entry to week 36 in % FVC in Study ALID-006 by Age Category

Age category	Laronidase/laronidase	n	Placebo/laronidase	n
6 - 12	2.1 ± 10.7	12	3.6 ± 6.6	10
13 – 18	- 1.3 ± 10.8	3	3.0 ± 7.7	8
19 – 43	-1.4 ± 2.9	7	- 0.3 ± 2.4	5

Reviewer's comment: The effect of laronidase in children younger than 12 years during the double blind study was clearly greater (6.6 %) than that seen in other subset analysis performed on these % FVC data. However, the same magnitude of % FVC increase could not be reproduced in the 10 children initially treated with placebo who were converted to laronidase for a 36 week period (3.6 % increase in mean % FVC). The reasons for this are not apparent. No conclusions regarding any favorable effects can be formed from these data.

Analysis by impairment. Table 34 shows the change in % FVC from baseline in Study ALID-003 to week 36 of Study ALID-006 based on quartiles of impairment at baseline.

Table 34. Change in % FVC from baseline to week 36 by impairment of % FVC at baseline

Impairment level	range % FVC	Laronidase/laronidase	n	Placebo/laronidase	n
least ↓ most	65.4 – 77.4	-1.2 ± 2.9	4	3.5 ± 8.1	7
	51.9 – 65.4	2.9 ± 7.7	6	0.4 ± 4.7	6
	41.6 – 51.9	4.1 ± 11.8	6	3.3 ± 3.9	5
	15.5 – 41.6	- 4.1 ± 8.2	6	3.1 ± 8.5	5

Reviewer's comment: No conclusion can be formed from the % FVC change according to quartiles of impairment at baseline.

Analysis of effect of anti-laronidase antibodies

20 of the 22 laronidase-treated subjects in the double blind study seroconverted as assessed by the RIP assay. An additional laronidase-treated subject seroconverted during the open label extension study. On the other hand 2 of the laronidase-treated subjects became seronegative at different timepoints during the open label study. The vast majority of laronidase-treated subjects that developed anti-laronidase antibodies remained seropositive for the duration of the study. From the 23 placebo-treated subjects in the double blind study, 21 seroconverted during the open label extension study, typically

between 4 and 8 weeks of laronidase treatment and remained seropositive for the 24 weeks of Study 006. In view of the high prevalence of anti-laronidase antibody positive subjects in both treatment groups, no meaningful comparisons can be made for the changes in % FVC during the extension study.

Analysis by Forced Vital Capacity independently of subject's age and height: The placebo-laronidase group had a mean (± SD) of 1.31 (± 0.52) L at Study 006 entry and 1.37 (± 0.53) L by week 36. The laronidase-laronidase group had a mean (± SD) of 1.25 (± 0.59) L at Study 006 entry and 1.25 (± 0.61) L by week 36. The change from baseline in Study 003 to week 36 of Study 006 in the laronidase/laronidase group was 0.1 L, whereas the change in the placebo/laronidase group was 0.07 L.

Reviewer's comment: These data parallel the observed effect of laronidase on the primary endpoint of % predicted FVC for the two treatment groups during the open label extension study, but within the raw pulmonary volumes data without any influence by factors needed to calculated the predicted FVC for the subjects age and height. These data stand in contrast with the small but significant gains in pulmonary volumes obtained during the double blind study 003 by the laronidase-treated group.

6 Minute Walk Distance

Primary Analysis

From entry to week 36 the mean change in the distance walked in the 6 minute walk test for the laronidase/laronidase group was an increase of 20.3 meters. This is approximately the same distance gained during the 26 weeks of the double blind study (19.7 meters). For this co-primary endpoint, the placebo/laronidase group demonstrated an increase in the mean distance walked of 32.4 meters from study entry to week 36. This change reverses the 18.3 meters decrease observed in this group from baseline to week 26 of the double blind study.

Table 35 shows the mean changes in the 6 minute walk test from baseline in the double blind Study ALID-003 to week 36 of the Open Label Extension Study ALID-006.

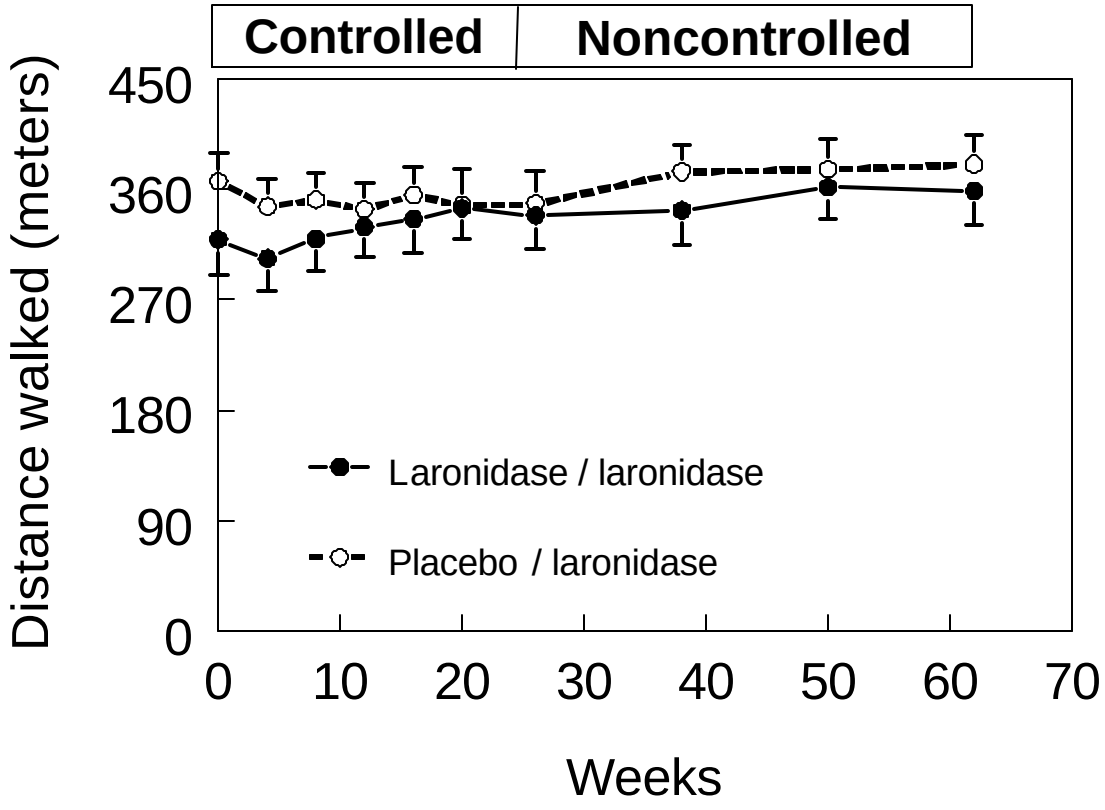
Table 35. Mean (± SD) changes in the 6 minute walk distance (meters) from baseline to week 36

	Laronidase/laronidase (n=22)	**Placebo/laronidase (n=23)**
Baseline	319.0 ± 131.4	366.6 ± 113.6
Entry	338.8 ± 127.1	348.3 ± 128.8
Week 36	359.0 ± 112.4	380.7 ± 127.0
Change from baseline to week 26 of Study 003	19.7	- 18.3
Change from entry into Study 006 to week 36	20.3	32.4

Prospectively defined exploratory analysis

Analysis by Study Visit: Both treatment groups increased their mean distance walked approximately to the same degree, although the placebo/laronidase group had most of the increase in the first 12 weeks of the extension study and the laronidase/laronidase group had a more substantial increase between weeks 12 and 24 of the extension study (Figure 11). No changes were noted in the last 12 weeks of Study 006 for both treatment groups.

Figure 11 shows the mean changes (± SEM) in the 6 minute walk distance across all timepoints in Study ALID-003 and ALID-006



Analysis by Study Center: No significant differences were observed across different clinical sites. Table 36 shows the mean changes in the distance walked in 6 minutes for each site.

Table 36. Mean changes (± SD) from entry to week 36 in 6 minute walk distance in Study ALID-006 by Clinical Site

	Laronidase/laronidase	n	Placebo/laronidase	n
1. United Kingdom	24.5 ± 54.5	6	44.8 ± 93.8	6
3. Germany	12.5 ± 38.1	4	30.8 ± 38.6	5
4. North Carolina	-13.7 ± 66.5	3	14.3 ± 103.0	3
5. New York	-42.3 ± 60.9	3	2.7 ± 47.8	4
6. Canada	69.5 ± 59.2	6	53.6 ± 26.9	5

Reviewer's comment: Here it is interesting to note that the 6 subjects originally randomized to Laronidase in the Canadian site had a mean change from baseline to the end of the double blind period of –16.8 ± 58.4, and in the open label extension had the greatest gain in distance walked in the 6 minute walk distance test. The biggest difference from the double blind study and the open label extension is seen in the placebo group studied in the United Kingdom: after a decline of 54.5 ± 74.9 meters in the 26 weeks of the double blind study, these 5 subjects had a mean increase of 44.8 ± 93.8 meters.

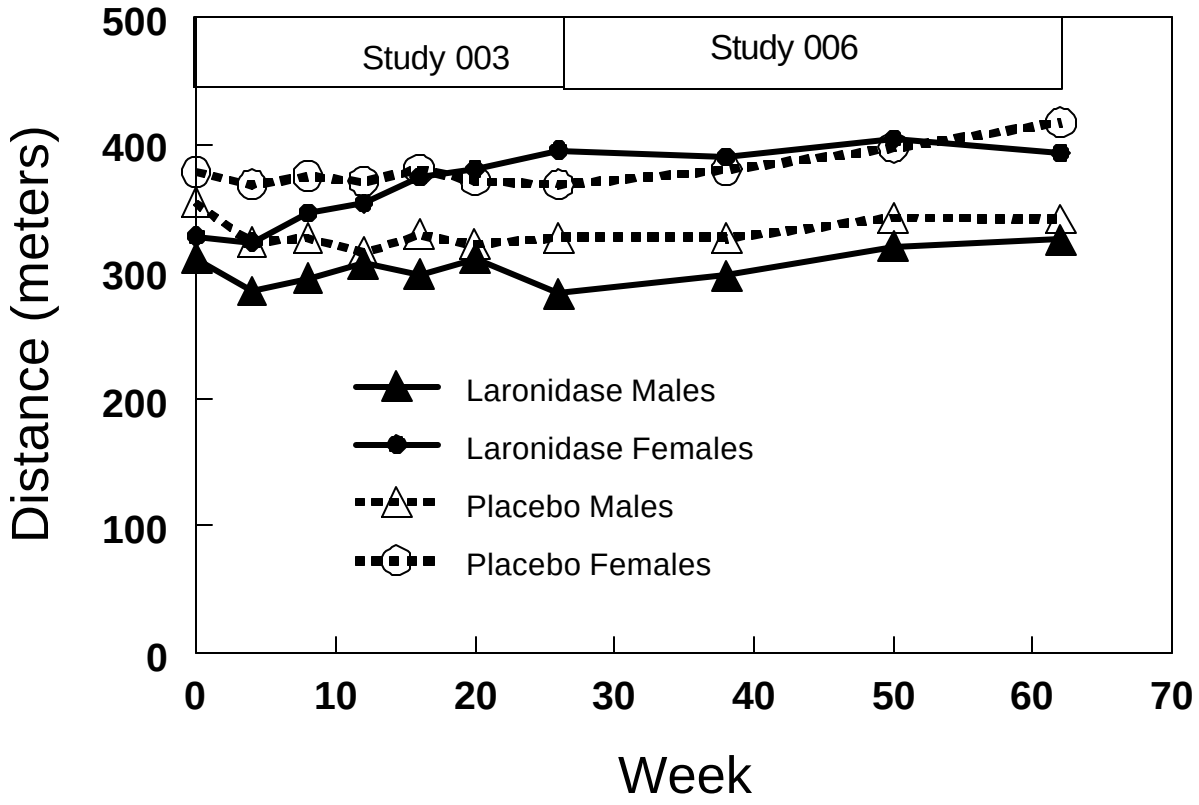
Analysis by Gender: Table 37 shows the mean changes in each site for males and females in both treatment groups

Table 37. Mean changes (± SD) from entry to week 36 in the distance walked in 6 minutes in Study ALID-006 by Gender

Gender	Laronidase/laronidase	n	Placebo/laronidase	n
Females	-2.2 ± 43.5	11	48.8 ± 76.1	12
Males	42.7 ± 72.9	11	14.4 ± 42.6	11

Reviewer's comment: The data in this extension study is different than that of Study 003, in which males in both treatment groups experiences a variable decrease of approximately 28 meters in the 6 minute walk distance, whereas laronidase-treated females had a remarkable mean increase of 67.5 meters in the 6 minute walk distance. In the 36 weeks of Study 006, placebo/laronidase female subjects and laronidase/laronidase male subjects had similar increases in distance walked, in contrast to the other subsets, in which no change was observed. The meaning of this observation cannot be determined in the absence of a control group.

Analysis by gender and study visit: Figure 12 shows the variation of the 6 minute walk distance by gender and treatment groups across the study visits.



Reviewer's comment: After an initial increase in distance walked by female subjects treated with laronidase, we observe stabilization of the distance over the additional 36 weeks for that subset. The female subjects initially randomized to placebo demonstrated a steady increase in distance walked over the 36 weeks of open label treatment with laronidase. Laronidase-treated males had a decline in distance walked from week 20 to week 26 in the double blind study 003, and had a gradual reversal of that decline during the 36 weeks of study 006. Placebo-treated males had a more modest increase (compared to the female counterparts) in distance walked during the 36 weeks of open label laronidase treatment.

Analysis by age group

Table 38 shows the effect of 36 weeks of laronidase in the 2 treatment groups of Study ALID-006 by age category.

Table 38. Mean changes (± SD) from entry to week 36 in 6 minute walk distance in Study ALID-006 by Age Category

Age category	Laronidase/laronidase	n	Placebo/laronidase	n
6 - 12	23.6 ± 52.8	12	23.9 ± 60.9	10
13 – 18	-41.3 ± 31.0	3	36.5 ± 80.6	8
19 – 43	41.0 ± 77.5	7	42.8 ± 45.9	5

Study 003 demonstrated a stronger effect on the distance walked in the younger subjects treated with laronidase. Study 006 shows a trend in the opposite direction, in which both treatment groups in the older subsets walk larger distances compared to younger subjects. However, no conclusion can be drawn from these small subsets.

Analysis by impairment

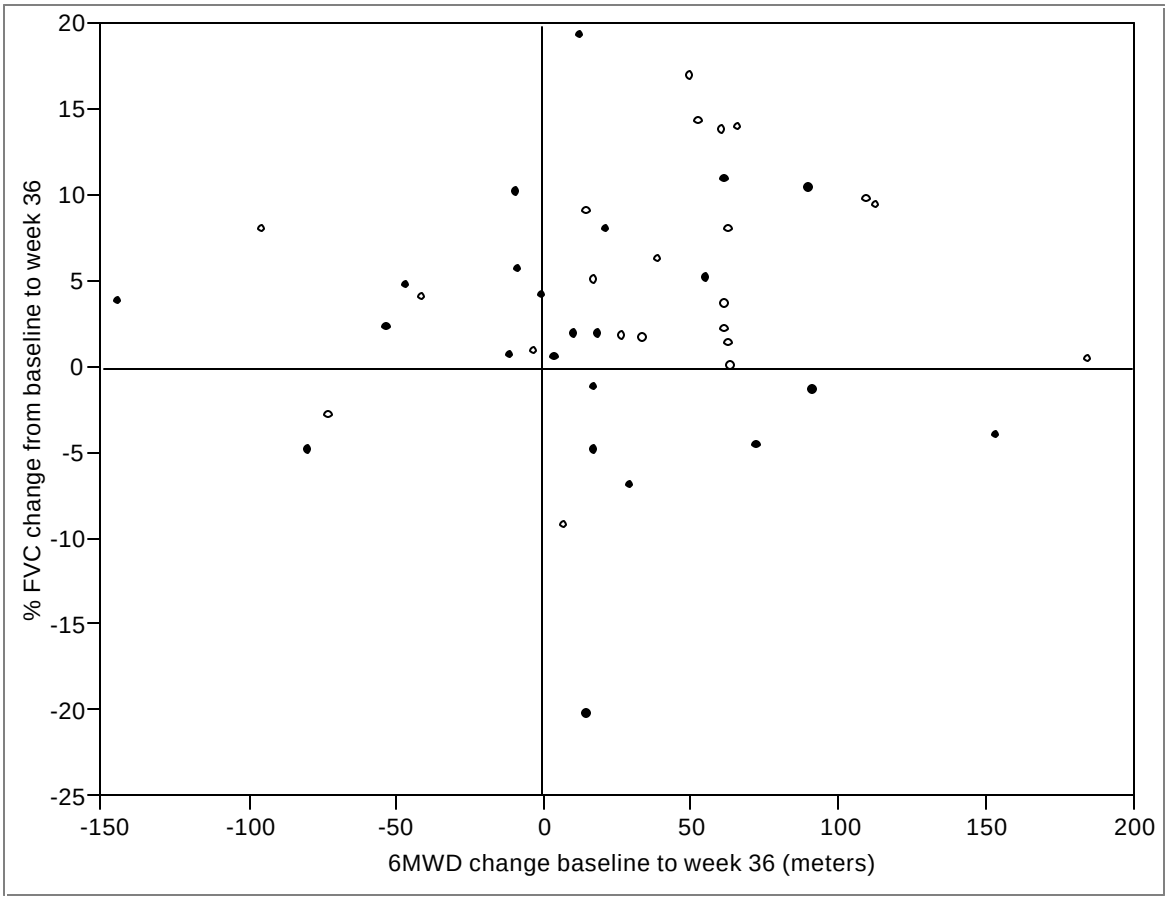
Table 39 shows the mean changes in the 6 minute walk distance for the 2 treatment groups by quartiles of mobility impairment at baseline.

Table 39. Mean changes (± SD) from entry in Study ALID-006 in the 6 minute walk distance at week 36 by the quartiles of impairment at Study ALID-003 baseline

Impairment level	Distance range	Laronidase/laronidase	n	Placebo/laronidase	n
least ↓ most	411 – 591	-19.7 ± 7.1	3	42.5 ± 52.6	8
	358 – 411	16.3 ± 79.7	7	26.2 ± 31.8	5
	276.5 – 358	50.6 ± 59.1	5	25.0 ± 111.5	6
	14 – 276.5	19.7 ± 59.8	7	31.0 ± 23.9	4

Reviewer's comments: No trends are apparent in any category of impairment at baseline.

Analysis by treatment effect in the change of % FVC from baseline: There is no correlation between the direction and magnitude of change from baseline to the end of Study ALID-006 between the data observed for % FVC and for the 6 minute walk distance (Figure 13).



Legend: Points shown as empty circles represent laronidase/laronidase-treated subjects and points represented as filled circles represent placebo/laronidase-treated subjects.

Analysis of effect of anti-laronidase antibodies

Table 40 shows the mean changes from entry into study ALID-006 to week 24 in the 6 minute walk distance for the 2 treatment groups in the anti-laronidase antibody positive groups, and individual values of 6 minute walk distance change in those few subjects that remained or became seronegative by week 24.

Antibody status	Laronidase/laronidase	n	Placebo/laronidase	n
Positive	26.6 ± 43.1	19	22.7 ± 62.1	20
Negative	-5, -2 , 11	3	31, 39	2

Duration of anti-laronidase antibodies as measured by RIP in subjects who seroconverted during the double blind study or during the open label extension did not correlate with changes in 6 minute walk distance in those timepoints corresponding to periods of seropositivity or seronegativity.

Secondary endpoints

Apnea Hypopnea Index

Primary analysis

In the ITT population that participated in the open label extension study, only small changes were noted. The double blind study 003 demonstrated a reduction in the apnea hypopnea index (AHI) for the laronidase treated group and no change for the placebo-treated group. During the open label extension study 006 the placebo/laronidase group experienced a change of the same magnitude as the laronidase group had shown, with a decrease of 3.5 events per hour in the AHI during the 24 weeks of study. However, the laronidase treated group did not demonstrate the same effect during the open label extension study 006 (Table 41).

Table 41. Mean changes (± SD) in the Apnea/hypopnea Index from baseline of Study 003 through Week 24 of Study 006

	Laronidase/laronidase	n	Placebo/laronidase	n
Baseline	21.4 ± 19.1	19	12.8 ± 11.2	21
Entry	18.2 ± 17.0	19	14.3 ± 13.8	19
Week 24	19.4 ± 21.6	19	10.6 ± 7.6	19
Change from baseline to entry	- 2.9	19	0.4	19
Change from entry to week 24	1.2	19	- 3.5	17

Exploratory Analysis

Sleep apnea at baseline: The sponsor prospectively defined an analysis of the subjects who had sleep apnea at baseline, pre-defined as AHI scores = 10 for children under 15 years of age and AHI scores = 15 for adult (older then 15 years of age) subjects. For this analysis, 11 subjects were identified in the laronidase/laronidase group and 9 subjects were identified in the placebo/laronidase group. In addition, the sponsor excluded subject 30806 from this analysis, with the rationale that he had severe sleep apnea with scores ranging from 60 to 100, and variations of the AHI scores within this range are not clinically meaningful, as they likely represent an artifact in the recording of these events. The data analysis in these subsets showed that subjects in the placebo/laronidase group had a mean reduction of 9.2 events per hour from entry into study 006 to week 24, after the mean increase of 2.5 events / hour during study 003. Subjects in the laronidase/laronidase group had an increase in the mean AHI score of 0.5 from study 006 entry to week 24, which basically maintains the initial improvement in AHI seen during study 003 (mean decrease of 6.3 events per hour), for an overall decrease of 5.5 events per hour from baseline of study 003 through week 24 of study 006. Among subjects with small number of apnea/hypopnea events, no changes from baseline and no differences between the 2 groups were seen.

Reviewer's comment: The rationale of studying the effect of laronidase on the AHI scores of subjects with sleep apnea at baseline is reasonable, and has clinical meaning. However, exclusion of subject 30806 from the 11 subjects in the laronidase/laronidase group may not be as appropriate; while subject 30806 is clearly an outlier, with a baseline index of 78.9, he contributed to the initial drop in the mean AHI score during the double blind study 003 (-9.1 from baseline to week 26) for the group and he was not excluded then. His AHI score increased from 69.8 at study 006 entry to 97.2 (a score increase of 27.4, the highest in the group) and is being excluded only for this analysis. Had he been included in the analysis, the laronidase/laronidase group with sleep apnea at baseline would have a mean increase of 2.9, rather than 0.5, events per hour.

A separate analysis was conducted to study the effect of laronidase in subjects with baseline AHI = 20. In the laronidase/laronidase subset with baseline AHI score = 20, the mean AHI (n=9) increased from 28.8 to 31.2 (a decrease from 23.6 to 23.0 if subject 30806 is excluded). Only 2 subjects in the placebo / laronidase group had AHI = 20 at baseline, and these 2 subjects had decreases in AHI scores of 18.9 and 18.4 events per hour.

Analysis by gender: Table 42 shows the effect of laronidase (mean ± SD) on the Apnea / Hypopnea Index in the 2 treatment groups by gender

Treatment Group	Gender	Baseline	n	Entry	n	Week 24	n
Laronidase/laronidase	Male	28.8 ± 22.2	10	26.3 ± 19.9	10	25.5 ± 26.4	11
	Female	12.1 ± 10.6	10	8.9 ± 5.4	10	12.9 ± 11.6	10
Placebo/laronidase	Male	22.7 ± 20.4	9	23.1 ± 19.3	8	13.0 ± 10.4	8
	Female	8.7 ± 4.9	12	9.9 ± 7.7	11	8.8 ± 4.6	11

Reviewer's comment: Males in both treatment groups had worse AHI scores at baseline as compared to females in both groups. The difference between the genders is higher than the possible treatment effect of laronidase. Nonetheless, in the double blind study 003, both male and female subjects in the laronidase-treated groups had similar improvement in AHI scores during the 26 weeks of treatment with laronidase. In the same study, males and females receiving placebo had similar degrees of worsening of AHI scores. In the open label extension study 006 most of the improvement seen in the placebo/laronidase group is driven by the males in the group. Similarly, albeit at a more modest scale, further improvement in AHI scores with additional 24 weeks of laronidase treatment are seen mostly in laronidase/laronidase males. The reasons for the gender difference are not apparent from the data.

Liver volume

Primary analysis

During the double blind study 003, the laronidase-treated group had experienced a mean 20 % reduction in liver volume, whereas the placebo-treated group had virtually no change in liver volume over the same 26 weeks of study. Table 43 shows the changes in liver volumes during study 006 and percentage changes for both treatment groups during studies 003 and 006.

Table 43. Mean (± SD) liver volumes (cc) and mean percentage changes (%) in liver volumes during Study 003 and Study 006 by treatment group

Parameter	Timepoint	Laronidase/laronidase	n	Placebo/laronidase	n
Liver Volume (cc)	**Baseline**	1211.2 ± 297.6	20	1358.0 ± 301.4	18
	Entry	998.8 ± 331.5	20	1300.6 ± 278.3	18
	Week 24	945.9 ± 286.4	20	1114.1 ± 256.5	18
% Change	**Baseline to Entry**	- 18.9 ± 19.4	22	1.3 ± 19.2	22
	Entry to week 24	- 3.6 ± 16.4	20	-12.6 ± 19.7	18

Reviewer's comment: Of the 18 laronidase-treated subjects with hepatomegaly at baseline, 13 achieved liver volumes in the normal range at the end of the double blind study (72%). During study 006, 2 more subjects with hepatomegaly continuing laronidase treatment had normalization of liver volumes. Also in the double blind study 003, of the 14 placebo-treated subjects with hepatomegaly at baseline, 3 achieved normal liver volume at the end of 26 weeks of study (21%). Of the remainder placebo-treated subjects, 5 had their liver volume normalized in the course of 24 weeks of the open label extension 006.

Similar to the findings of liver volume reduction seen for the Phase 1 / 2 study CL-IDU-001, most of the reduction in volume for the laronidase-treated group took place during the first 6 months of therapy. During the open label extension, only an additional mean 3.6 % reduction was observed. The surprising finding during study 006 was the lower magnitude of liver reduction in the placebo-treated subjects that switched to active treatment (12.6 % compared to 18.9 %).

Shoulder flexion

Primary analysis

During the double blind study 003, the placebo-treated group experienced a slight worsening of the shoulder flexion, equivalent to that observed in the laronidase-treated group. Both treatment groups experienced similar degrees of very mild improvements during the open label extension study 006 (Table 44).

Table 44. Mean (± SD) shoulder flexion range of motion (degrees) and changes during Study 003 and Study 006 by treatment group

Timepoint	Laronidase/laronidase	n	Placebo/laronidase	n
Baseline	96.1 ± 30.2	19	89.8 ± 24.0	23
Entry	88.9 ± 37.7	22	85.2 ± 32.7	23
Week 24	94.7 ± 26.1	22	91.5 ± 24.1	23
Baseline to Entry	- 1.5 ± 30.4		-4.9 ± 27.6	
Entry to week 24	5.8 ± 21.2		6.3 ± 20.8	

Reviewer's comment: These data demonstrate that laronidase did not show any clinically meaningful effect on shoulder flexion range of motion, and the effect of unblinding during study 006 was most likely responsible for the 6 degrees improvement seen in both treatment groups. Even this change seen during study 006 is unlikely to be perceived as being a meaningful benefit in shoulder motion.

Analysis by impairment (shoulder flexion range of motion above and below the median for the overall group at baseline of study 003) was also inconclusive.

Disability Index

Primary Analysis

The CHAQ/ HAQ Disability Index evaluates the extent of disability on a scale of 0 to 3, with 3 being the worst score.

Table 45 shows the mean (± SD) shoulder flexion range of motion (degrees) and changes during Study 003 and Study 006 by treatment group

Timepoint	Laronidase/laronidase	n	Placebo/laronidase	n
Baseline	2.0 ± 0.49	21	1.9 ± 0.6	22
Entry	1.9 ± 0.58	21	1.8 ± 0.73	22
Week 24	1.7 ± 0.54	21	1.6 ± 0.8	22
Baseline to Entry	- 0.1		- 0.1	
Entry to week 24	-0.2		- 0.2	

These changes through 50 weeks of study (combined Studies 003 and 006) were very small, and were similar for both treatment groups.

Tertiary endpoints

Urinary GAG's

After the 54 % reduction in urinary GAG concentration noted in the laronidase-treated group during Study 003, an additional 20 % reduction occurred in this group during the open label Study 006. The placebo-treated group had a mean 47 % increase in urinary GAG concentration during Study 003, and had a 68.9 mean reduction when switched to laronidase treatment during the open label extension 006. At baseline in Study 003 and at entry into Study 006 all subjects in both treatment groups had abnormal urinary GAG concentrations. At week 24, 6 of the 22 subjects in the laronidase/laronidase group had normal GAG levels, and 3 of the 23 subjects in the placebo/laronidase group had normal GAG levels.

Total respiratory event index and total sleep time with hypoxemia

The placebo/laronidase group had a small improvement in this index (16.6 ± 14.0 at study 006 entry to 13.0 ± 7.8 at week 24) compared with the laronidase/laronidase group, with a small degree of worsening during Study 006 (from 19.7 ± 16.8 at study entry to 21.9 ± 21.4 at week 24). No significant changes were also noted for either treatment group for the time spent with oxygen saturation below 90 % during sleep.

Pain scale

The pain scale component of the CHAQ / HAQ reflects partially the functional status of the subjects, with a lower score indicating less pain. The scale range is 0 to 3. The mean change from entry to week 24 for the placebo/laronidase group was – 0.3 and the mean change for the laronidase/laronidase group during the same period was 0.1. Over the course of the 50 weeks of Study 003 and 006 combined small improvement in the degree of pain was noted for both groups.

Reviewer's comments: Assessment of pain in a scale, even with appropriate methodology, validated scales and measures to prevent bias, is difficult to accomplish without taking into account the concomitant use of drugs or physical measures to relieve

pain. In addition, the pain here relates to a variety of causes, ranging from arthritic pains to headaches related to sinusitis or increased intra-cranial pressure. In this context, evaluation of changes in perception of pain of a multifactorial nature is difficult.

Joint Range of Motion

For shoulder extension and for knee flexion higher values of ROM reflect less severe disease. For knee extension, more negative values reflect more severe disease. Table 46 shows only modest improvements or no change for the joint range of motion in the 3 joint groups assessed for both treatment groups.

Table 46. Mean ± SD during Studies 003 and 006 for Joint ROM for the 2 treatment groups

Joint		Laronidase/laronidase	n	Placebo/laronidase	n
R Shoulder extension	Baseline	22.9 ± 13.3	18	28.9 ± 14.1	23
	Entry	27.7 ± 10.7	20	27.0 ± 8.6	23
	Week 24	29.8 ± 14.0	20	32.2 ± 11.2	23
L Shoulder extension	Baseline	25.6 ± 10.6	18	28.0 ± 12.2	23
	Entry	27.7 ± 9.6	20	27.1 ± 6.9	23
	Week 24	29.4 ± 13.1	20	30.3 ± 11.9	23
R Knee extension	Baseline	- 12.1 ± 13.4	19	- 14.3 ± 16.3	23
	Entry	- 9.0 ± 11.5	22	- 15.6 ± 16.7	23
	Week 24	- 6.2 ± 9.8	22	- 12.4 ± 16.3	23
L Knee extension	Baseline	- 12.3 ± 13.8	19	- 15.3 ± 17.1	23
	Entry	- 9.5 ± 11.9	22	- 14.9 ± 16.6	23
	Week 24	- 6.3 ± 12.1	22	-12.6 ± 15.4	23
R knee flexion	Baseline	106.7 ± 19.9	20	114.4 ± 11.3	23
	Entry	115.1 ± 18.0	22	118.6 ± 12.3	23
	Week 24	116.1 ± 17.1	22	118.3 ± 15.1	23
L knee flexion	Baseline	107.4 ± 20.3	20	117.0 ± 11.4	23
	Entry	116.6 ± 17.0	22	118.5 ± 15.7	23
	Week 24	117.7 ± 16.6	22	119.9 ± 15.6	23

Global Components of CHQ or SF-36

The CHQ was used to assess global components for each subject. A parent or caregiver completed one section of the questionnaire (CHQ-PF50), and the child completed another part (CHQ-CF-87). Higher scores reflect better responses. In addition, parents evaluated their own QoL by using SF-36. In the latter instrument, higher scores also reflect better

responses. No conclusion can be drawn from the data and there were no differences between the 2 treatment groups.

Growth Velocity

Changes in height were assessed in pre-pubertal children through Studies 003 and 006. Subjects who have not reached Tanner Stage 2 by Week 24 of the open label study were included. Normal pre-pubertal height increase is approximately 5 cm per year. As mentioned in the report for Study 003, too few pre-pubertal subjects had more than one historical standing height for calculation of pre-study growth slope values. After completion of Study 003, some of the pre-pubertal subjects entered puberty during the 24 weeks of the open label extension. Some of the growth in height can also be attributed to release of joint contractures, particularly in the knees, rather than a true effect on linear growth.

Laronidase/laronidase group: Seven subjects randomized to laronidase during Study 003 had a mean growth of 4.7 cm. Two of these subjects entered puberty during Study 006. The remainder 5 pre-pubertal children had grown a mean of 4.6 cm from baseline in Study 003 to week 24 of Study 006. The mean growth from entry into Study 006 until Week 24 for these 5 children was 0.4 cm.

Placebo/laronidase group: Seven subjects randomized to placebo during Study 003 had a mean growth of 2.7 cm. Three of these subjects entered puberty during Study 006. The remainder 4 pre-pubertal children had grown a mean of 4.9 cm from baseline in Study 003 to week 24 of Study 006. The mean growth from entry into Study 006 until week 24 for these 4 children was 1.7 cm.

Visual acuity, ophthalmologic and slit lamp exam, tonometry, fundoscopy

Fundoscopic examination: From the subjects that had baseline and/or study 006 entry abnormal fundoscopic findings, the proportion of shifts to a normal fundoscopy were identical in the 2 treatment groups: 1 left eye and 1 right eye shifted from abnormal to normal in each of the treatment groups.

Slit lamp measurements: No shifts were observed from abnormal to normal during study 006 in either treatment group. In each group, 1 subject (one eye) shifted from normal to abnormal slit lamp findings.

Visual acuity: No conclusion on the laronidase effect can be formed from the visual acuity data assessed with the Snellen chart.

Tonometry: Most subjects in both treatment groups had normal eye pressures at Study 003 baseline and at Study 006 entry. Shifts from abnormal to normal or vice versa were too few and no conclusive effect of treatment can be assessed from the data.

Cardiac Function

No clinically significant changes were observed in the electrocardiographic tracings in subjects of both treatment groups during the 24 weeks of Study 006.

There were only 2 clinically significant echocardiographic changes during Study 006: one subject in the placebo/laronidase group had mild pericardial thickening at week 24 which was not present at study entry, and one subject on the laronidase/laronidase group had moderately enlarged left atrium, a finding also not present at study entry.

Forced expiratory volume in one second

No mean changes were seen in either treatment group in the FEV1 from baseline to study 006 entry or from study entry to week 24.

Total Lung Capacity

No mean changes were seen in either treatment group in the TLC from baseline to study 006 entry or from study entry to week 24.

Diffusing Capacity

No mean changes of clinical significance were seen in either treatment group in the diffusing capacity from baseline to study 006 entry or from study entry to week 24.

Heart rate, respiratory rate and O2 saturation

No mean changes of clinical significance were seen in either treatment group in the heart rate, respiratory rate or in O_2 saturation from baseline to study 006 entry or from study entry to week 24.

Safety

AE's

This study report covers the first 24 weeks of the ongoing Study 006, in which 22 subjects that had received laronidase for 26 weeks in the double blind study 003 continued to receive laronidase treatment in an open label fashion (laronidase/laronidase group), while the 23 subjects initially randomized to placebo during the double blind study 003 were switched to laronidase treatment (placebo/laronidase group).

AE's in study 006 are defined as having begun at the time of enrollment in the Open Label Study through Week 24, or that began during the Double Blind Study (003) and worsened during the 24 weeks of Open Label Extension.

All subjects in both treatment groups experienced at least 1 AE during the study. One subject in the placebo/laronidase discontinued treatment due to a SAE, and one subject chose to discontinue treatment at week 24. Drug possibly, probably or definitely related AE's were reported in 11 (48%) placebo/laronidase subjects, and in 10 (45%) laronidase/laronidase subjects. Among the latter, infusion associated reactions (IAR's) occurred in 7 (30%) placebo/laronidase subjects and in 8 (36%) laronidase/laronidase subjects. IAR's were defined as all drug-related AE's occurring on the day of infusion, except for those identified by protocol required assessments prior to the infusion.

Three subjects (13%) among the placebo/laronidase group reported severe AE's (one with respiratory distress, one with chronic bronchitis, tracheitis, and myocarditis seen at autopsy and one with chocking), and 1 laronidase/laronidase subject reported a severe AE (abnormal vision).

All AE's with incidence higher than 30 % in either treatment group during the open label extension Study 006 were reported according to WHO-ART terminology and identified by the Preferred Term. Headache was the most commonly reported AE, with 57% and 45% incidence in the placebo/laronidase and the laronidase/laronidase groups, respectively, followed by rhinitis (43% and 41% in placebo/laronidase and laronidase/laronidase groups, respectively). Coughing and pharyngitis followed with approximately 30 % of

subjects reporting these events, with similar frequencies among the 2 treatment groups. Gastrointestinal AE's were more prevalent in the placebo/laronidase group, with 16 subjects (70%) reporting events, contrasted with 10 (45%) reporting in the laronidase/laronidase group. The specific events = 30 % were nausea, diarrhea and vomiting.

In comparing the incidence of the AE's with incidence = 30% within each treatment group between Studies 003 and 006, the 23 placebo-treated subjects experienced a reduction in these AE's as they were treated with laronidase during the 24 weeks of the open label study. The incidence of these most frequent AE's in the laronidase group during the double blind study remained the same during the open label study.

AE's that were possibly, probably or definitely related to study treatment were reported with similar frequency in the placebo/laronidase group (48 %) and the laronidase/laronidase group (45 %). From these, the most common (defined by the sponsor as > 1 subject) in the laronidase/laronidase group were arthropathy (14 %) and flushing (14 %), and in the placebo/laronidase group were arthralgia (9 %) and leg pain (9 %).

IAR's were observed in similar proportions in both treatment groups. The most frequently reported IAR in both treated groups was flushing (1 / 23 placebo / laronidase subject and 3 / 22 laronidase/laronidase subjects. The majority of these IAR's (flushing, rash) were reported as mild. 3 / 23 placebo/laronidase subjects and 2 / 22 laronidase/laronidase subjects with IAR's required medication with antipyretics and / or antihistamines. None required drug infusion rate decrease or interruption, or use of steroids.

The protocol called for IgE and complement testing in subjects experiencing moderate or severe IAR's. 3 subjects in the placebo/laronidase group with moderate IAR's were not tested (protocol deviation).

Data from AE's related to study drug occurring in non-infusion days was inconclusive, as most AE's under specific preferred terms were observed in single subjects (here again GI symptoms are more common in the placebo/laronidase subjects).

Deaths and SAE's

One subject (30502) in the placebo/laronidase group died at Week 16 of Study 006 of complications from upper respiratory tract infection and bronchitis. This subject, a 7 year old male, had a history of central and obstructive sleep apnea and was offered tracheostomy by the investigator, which the parents had not yet consented by the time of the event. Six days after infusion 16, the subject was found dead in his bed at home. Autopsy findings revealed marked chronic tracheo-bronchitis with possible acute exacerbation with sepsis. This SAE is unrelated to study drug.

Subject 10909 (placebo/laronidase) is a 10 year old female was hospitalized for 1 day after the 8th week in Study 006 for the surgical placement of a vascular access device, due to the difficulty in obtaining peripheral venous access for laronidase administration. This SAE is unrelated to study drug.

Subject 30101 (placebo/laronidase) is a 29 year old female admitted to the hospital after the 5th infusion of laronidase for repair of a recurring umbilical hernia repaired initially several years prior to entry into this study. This SAE is unrelated to study drug.

Subject 30309 (placebo/laronidase) is a 17 year old male status post heart transplantation was hospitalized after the 21st infusion in Study 006 with dyspnea, tachypnea and tachycardia. After transfer to a national heart center, chronic rejection was detected through a heart biopsy, and the immunosuppressive regimen was increased, with improvement in the symptoms and discharge after 3 weeks. This SAE is unrelated to study drug.

Subject 50807 (placebo/laronidase) is a 14 year old female experienced a chocking episode while eating a candy after 17 weeks into Study 006. The episode resolved with a back thrust within 5 minutes, without sequelae. This SAE is unrelated to study drug.

Subject 60607 (placebo/laronidase) is a 15 year old male with history of severe lung restriction, cardiac involvement and anxiety who reported nausea and lightheadedness after the 11th infusion of laronidase, resolving spontaneously. At the 12th infusion, the subject had respiratory distress with hyperventilation and decreased oxygen saturation. The investigator treated the subject for possible atelectasis and anxiety, with improvement. This initial SAE was reported as remotely associated with the study drug. From April 8, 2002 until October 16, 2002 the same subject developed intermittent but progressively worse episodes of urticarial rash and hypoxemia, despite higher doses of anti-histamines and the use of intravenous corticosteroids. His April 2002 plasma complement activation results and IgE were positive, but with a negative skin testing with the enzyme.
On October 16, 2002 (extension week 62), three hours after starting the infusion, the subject developed a rash with "facial flushing" and hypoxemia necessitating biPAP and then oxygen. The infusion was apparently stopped and Solu-Medrol administered. Soon thereafter, intermittent apnea developed and the subject was transported to an ER where he was noted to be cyanotic with "urticarial lesions extending from the face to the groin area." The subject's airway could not be maintained, attempts at oral intubation were unsuccessful and an emergency cricothyroidomoty was performed. During this time, the subject was bradycardic and epinephrine was administered. Following tracheostomy, initial blood gases showed hypoventilation and hypoxemia. The subject was transported to the ICU where he is reported to be stabilizing. The neurological status is unknown to the sponsor. The investigator reported the events as "definitely related to study medication." Notably, during the open label extension, obstructive sleep apnea was diagnosed and CPAP was prescribed but the subject was intolerant of it and intermittent nocturnal oxygen was prescribed instead along with periodic use of biPAP.

Subject 30608 (laronidase/laronidase) is a 7 year old female who had a hospitalization for otitis media during the baseline period of Study 003, underwent a tympanoplasty after week 7 on Study 006. This SAE is unrelated to study drug.

Study 30806 (laronidase/laronidase) is a 44 year old male whose SAE was described in Study 003. In summary, patient had complications of aortic valvuloplasty, including cardiac arrest and sepsis, but made full recovery during Study 003. He was hospitalized due to worsening of palpitations after week 21 into the Open Label Extension study. No

abnormalities were uncovered despite extensive assessments and the subject was discharged without specific treatment. This SAE is unrelated to study drug.

Subject 50706 (laronidase/laronidase) is a 15 year old female was hospitalized after 6 weeks into the study for elective surgical placement of a Port-A-Cath for venous access. The subject was discharged the following day without sequelae. This SAE is unrelated to study drug.

Clinical Laboratory Evaluations

No clinically relevant changes were observed for any mean serum chemistry values over the 24 weeks of Study 006.

From the hematologic parameters, platelet counts showed a trend to increase with laronidase treatment. Table 47 shows the mean ± SD changes in platelet counts from baseline into Study 003 to week 24 of Study 006.

Table 47. Mean ± SD changes in platelet counts from baseline into Study 003 to week 24 of Study 006.

Timepoint	Laronidase/laronidase	n	Placebo/laronidase	n
Baseline	218 ± 52	22	236 ± 66	21
Entry	253 ± 72	22	212 ± 47	21
Week 24	284 ± 83	22	271 ± 44	21

Reviewer comment: These changes occurred within the normal range of platelet counts. However, there is a suggestion that laronidase treatment resulted in the increments in platelets. The placebo/laronidase group had a decrease in platelet counts during Study 003, but upon treatment with laronidase had a mean increase of 58.7 X 10^3/µL. A possible interpretation of these data is that decreases in spleen size (such as those observed during the Phase 1 study) would cause a parallel reduction in platelet removal and destruction. This hypothesis is physiologically plausible, but unproven, particularly given the lack of spleen volume changes in both Studies 003 and 006.

No clinically relevant changes were observed for any mean parameters assessed by urinalysis over the 24 weeks of Study 006.

Vital signs and physical findings

No clinically relevant changes were observed for vital signs and physical examination findings over the 24 weeks of Study 006.

ECG and Echocardiogram findings

Two subjects in the placebo/laronidase group had echocardiographic changes summarized in this review under D. Results: 6. Tertiary Endpoints: h. Cardiac Function.

Other findings

Forty of the 45 subjects participating in the Open label Extension Study 006 had developed IgG antibodies confirmed by RIP. 21 / 23 placebo/laronidase seroconverted during the open label study 006. Twenty of the 22 laronidase-treated subjects were IgG (+) at study 006 entry. One laronidase-treated subject developed IgG antibodies during the Open label extension. Two laronidase / laronidase subjects became IgG negative after a relatively long period of IgG seropositivity, during study 006. By week 24, 19 laronidase/laronidase treated subjects were IgG (+). No correlation between AE's or IAR's could be established with the IgG antibody status, given the few numbers of IgG (-) subjects in both treatment groups.

Summary

Study 006 was conducted as an uncontrolled open label extension trial of laronidase in the 45 subjects that participated in the Double blind randomized, placebo-controlled Study 003. The 22 subjects assigned to laronidase and the 23 subjects assigned to placebo weekly intravenous infusions during Study 003 all received the same weekly dose of laronidase (100 U / kg) for a period of 36 weeks. Except for the two co-primary endpoints, 24 weeks of data collected and analyzed are included in this BLA submission. For the two co-primary endpoints, 36 weeks of data are presented. However the study is ongoing, with long term safety data being collected.

The % FVC, a co-primary endpoint in this study, showed no changes for the laronidase/laronidase group (maintenance of the increment achieved during Study 003) and smaller changes for the placebo/laronidase group as compared to the laronidase group in Study 003. This observation cannot be explained on the basis of the small but statistically significant improvement in % FVC seen in the laronidase-treated group during Study 003.

The 6MWD test, the other co-primary endpoint in the study, showed marginal increments in the distance walked in 6 minutes, with a 20 meter increase in the laronidase/laronidase group and a 32 meter increase in the placebo/laronidase group.

The trend seen during Study 003 of more marked increments in these endpoints in the young, female subset with less severe disease at baseline is not reproduced here. Data from secondary and tertiary endpoints was inconclusive, with the exception of the reduction noted in urinary GAG concentrations and in the liver volume.

Summary of Efficacy

MPS I is a complex disorder characterized by progressive accumulation of glycosaminoglycans in multiple tissues and organs, at different rates for different individuals. Therefore, the development of laronidase for the treatment of patients with MPS I could not be restricted to the effect of the product on one single clinically meaningful endpoint. Based on in vitro binding studies in human MPS I fibroblasts and pre-clinical experience with appropriate canine and feline models of MPS I, a dose of 100 U / kg of laronidase to be given intravenously on a weekly basis was selected for all the clinical development of this product.

An open label, uncontrolled Phase 1 trial of laronidase was conducted in a group of 10 subjects with MPS I, 8 of whom had the Hurler-Scheie form (intermediate severity and progression to death). In this group of subjects, laronidase treatment reduced liver and spleen volumes and significantly reduced urinary GAG's in a matter of a few weeks. The effect of laronidase on other endpoints of clinical significance to patients with MPS I was variable, with a much smaller magnitude. Specifically, assessments related to cardiac function, muscle-skeletal, airway and central nervous system function suggested an overall favorable trend, but it is imperative to note that these data obtained from an open label uncontrolled study cannot provide support for laronidase efficacy in MPS I.

The main support for a Biomarin claim of efficacy comes from a single randomized, placebo-controlled, multicenter trial of laronidase at 100 U / kg weekly vs. placebo in a group of 45 subjects with MPS I for 26 weeks. The two primary endpoints selected were the difference in percent of predicted FVC (% FVC) change from baseline to week 26 between the treatment groups and the difference in the distance walked in 6 minutes (6MWD) change from baseline to week 26 between the 2 treatment groups. In order to explore the effect of laronidase in other important clinical areas affected in MPS I secondary and tertiary endpoints were chosen. Parameters assessing sleep apnea, joint range of motion, liver volume, pain scores, heart function, degree of disability and urinary GAG's were assessed and the data analyzed to provide additional support for the effect in the primary endpoints. Similar to the distribution of subjects in the Phase 1, most were patients with the Hurler-Scheie syndrome. In order to participate in the study, subjects with established diagnosis of MPS I had to be older than 5 years, and have a baseline % predicted FVC of less than 80 %. The rationale in using the latter was that studying subjects with some impairment of pulmonary function would provide better chance of demonstrating a favorable effect. The inclusion criteria for the study did not call for baseline impairment in the 6MWD.

Twenty two subjects were randomized to laronidase and 23 subjects to placebo. The 2 groups complied with study agent administration and study visits. After 26 weeks the laronidase group had a 4.9 % increase from baseline in the % FVC, whereas the placebo group had a 0.7 % decrease in % FVC, with the % FVC calculated on the basis of the baseline height of the subjects, as opposed to the height determined at the time of each monthly visit when pulmonary functions were assessed. The difference was statistically significant, but was only marginally meaningful.

In the 6 MWD, the laronidase group walked a mean 19.7 meters more at week 26 than at baseline, whereas the placebo group walked a mean of 18.4 meters less than at baseline. The difference in mean change from baseline to week 26 (38.1 meters) did not reach statistical significance. Subset analysis in both co-primary endpoints revealed a more favorable trend in female subjects, younger and with less severe disease.

With regard to secondary and tertiary endpoints, no general conclusions could be drawn. The data is clearly favorable to reductions in liver volume and urinary GAG's, as seen in the Phase 1 study. Laronidase effect on clinically relevant parameters of the sleep study was not clinically or statistically significant. An exploratory subset analysis showed a favorable trend in subjects with sleep apnea. A favorable effect of laronidase compared to placebo could not be demonstrated in other endpoints in the study.

The Phase 3 trial was followed by an Open Label Extension study. All 45 subjects that took part in the Phase 3 trial are currently receiving the same laronidase dose used for the laronidase group in the controlled trial, and the study is currently ongoing. Data from the first 24 weeks was collected, analyzed and submitted with this submission, as well as the first 36 weeks of data on the two co-primary endpoints. By week 36 of the Open Label Extension study, the mean % FVC has not changed for the 22 subjects continuing on the same laronidase treatment and increased only by a mean of 2.6% in the 23 subjects who were switched to laronidase. These data cannot be explained on the basis of individual variations or seasonal changes. In the 6 MWD, the 22 subjects originally assigned to laronidase treatment were able to walk an additional mean of 20.3 meters at week 36 of the extension study (40 meters in the 50 weeks of laronidase treatment), whereas the placebo/laronidase group was able to walk a mean of 32.4 meters more at week 36 compared to the entry into the open label study. Again, no conclusion can be drawn from these uncontrolled and unblinded data with a small clinical effect. The Apnea/hypopnea index (AHI) showed a small reduction in apneic events with 24 weeks of laronidase treatment for the subjects originally allocated to placebo in the Double Blind Study, without any change in the AHI for the subjects that continued on laronidase treatment during the Open Label Extension. The subset of subjects with sleep apnea at baseline who were switched from placebo to laronidase treatment during the Open Label Extension demonstrated a mean decrease of 9.2 events per hour of sleep at week 24. The parallel group of subjects with baseline sleep apnea continuing on laronidase for an additional 24 weeks of Open Label Extension had unchanged mean AHI scores. Liver volume was reduced by a mean of 12.6 % and urinary GAG levels by a mean of 69 % in the placebo subjects undergoing 24 weeks of laronidase treatment. Other secondary and tertiary endpoints during the Open Label Extension demonstrated no changes within the 24 week period analyzed.

Antibodies against laronidase formed in most subjects, and no conclusion regarding the impact of these antibodies on efficacy can be formed.

Summary of Safety

Any safety analysis of a product studied in MPS I must be performed in light of the background of significant morbidity that is associated with the enzyme deficiency. Almost all subjects that participated in the Phase 1 or the Phase 3 studies had experienced at least one adverse event (AE). The safety database is 59 subjects exposed to laronidase for variable periods of time, with a minimum of 24 weeks for the placebo subjects switched to laronidase in the Open Label Extension to more than 3 years for the subjects that are still being treated with laronidase infusions under the Phase 1 protocol.

The safety of laronidase treatment can be best assessed by looking at the Phase 3 Double Blind Randomized Controlled study 003 data. This approach minimizes to the extent possible the influence of the severity of the disease itself. In that study the overall rate of AE's was very similar between the 2 treatment groups. Infusion associated reactions (mostly flushing and rash) were equally similar in the 2 groups, despite the fact that almost all laronidase-treated subjects developed antibodies against the enzyme. Two notable exceptions to the lack of correlation of presence or levels of anti-laronidase antibodies and frequency of AE's are subject 008 that participated in the Phase 1 study and subject 60607 in the Phase 3 study. The former died from a possible viral illness that led to respiratory distress and respiratory arrest. In that subject anti-laronidase IgG antibody titers were high, and there was evidence of immune complex deposition in glomerular capillaries without any histopathological changes. A link between this finding and the worsening of the subject's severe pulmonary involvement cannot be ruled out. The latter (subject 60067) developed progressively worse episodes of hypoxemia and rash a few weeks after being switched from placebo to laronidase treatment during the Open Label Extension study. These events occurred in the face of positive anti-laronidase IgE levels and plasma complement activation, and 5 months after the initiation of laronidase culminated with an anaphylactic reaction necessitating an emergency cricothyroidomoty. This particular subject also had a lower than the group mean response in both primary endpoints, as well as 9 % reduction in liver volume and an 11 % reduction in urinary GAG. Therefore subject 60607 AE and serologic profile calls for careful selection, monitoring, and pre-medication or desensitization of certain MPS I patients to be treated with laronidase after the product's approval for marketing. The event also raises the issue of evaluation of a reproducible and reliable anti-laronidase IgE test to be used in conjunction with laronidase treatment for marketing.

Another death in the Phase 1 study and a death occurring in the Open Label Extension were clearly unrelated to laronidase treatment. Subject 002 died as a result of spinal cord injury after spinal fusion surgery after more than 2 years in the study. Subject 30502 in the placebo/laronidase group died at Week 16 of Study 006 of complications from upper respiratory tract infection, bronchitis and sepsis. All other SAE's reported were related to the morbidity of MPS I and not to laronidase treatment.

Conclusions and Recommendations

The studies presented in the submission demonstrate substantial evidence of efficacy of laronidase in the treatment of patients with MPS I. However, these data are limited in both statistical strength and in clinical significance. The weight of this conclusion derives from

the Phase 3 double blind study 003, which shows a statistically significant, but clinically modest, change in % FVC in the laronidase group as compared to placebo control. The other co-primary endpoint, the 6 minute walk test, did not reach statistical significance for a treatment-associated difference, but had a favorable trend for laronidase.

Exploratory analyses of the data suggest that the benefit of the treatment, if any, may not be homogeneous across the MPS I subjects. A subset of females and/or younger subjects and/or those with less severe disease may be more prone to benefit. However, in addition to being post-hoc exploratory analyses, there are few subjects in these studies, and these factors cannot be readily isolated for examination. Consequently, firm conclusions regarding subsets more or less appropriate for treatment with this dose and regimen may be unfeasible.

Two markers of in vivo enzyme activity were associated with significant reductions during the 26 weeks of Study 003: liver size reductions and urinary GAG concentration. The response of these markers to laronidase has been consistently shown also in the pre-clinical experiments and in the Phase 1 clinical trial, as well as in the placebo-treated subjects switched to laronidase treatment during the Open label Extension. However, these markers cannot be viewed as surrogates for improving clinical endpoints that contribute to the morbidity and untimely mortality of MPS I.

Possible reasons for non-robust indications of clinical benefit may include inadequate knowledge regarding dose regimen-response, so that an optimal dose and regimen was not evaluated in these studies, insufficient duration of the controlled study to permit robust demonstration of efficacy, and possibly selection of a patient population less susceptible to benefits on the parameters examined than a different portion of the disease patient population. Another factor that may have contributed to a less robust evidence of clinical benefit was the near universal formation of antibodies against laronidase. While these antibodies were not shown to be neutralizing in in-vitro assays, their presence raise questions about long term effects on the efficacy of the product, as well as the safety.

The many questions remaining on the safety and efficacy profiles of laronidase for the treatment of patients with MPS I can be best answered by additional studies, in which dose-response relationships and clinical effects from a more prolonged duration can be adequately investigated.

Given the lack of alternative treatments in a rare disease with severe or fatal consequences, this reviewer recommends approval of laronidase, supported by the evidence of efficacy in the co-primary endpoints and favorable trends in subsets of MPS I in secondary endpoints. Post-marketing commitments will be necessary to provide clearer understanding of the long-term effects of laronidase in patients with MPS I. These include studies of the effect of different doses and dosing regimens on markers of the disease and subsequently on endpoints with a clinically meaningful benefit. These or other studies will need to explore the relationship of anti-laronidase antibody development on the long term benefits of laronidase and the overall safety and AE's. Establishment of a patient registry to learn about the long term experience with laronidase will be beneficial to understand the effects of laronidase on the natural history of MPS I in a wider subject population, such as those patients younger than 5 years of age. Careful selection of the specific population to

benefit from the treatment based on the knowledge gained in the development of laronidase needs to be undertaken. After analysis of the data in this submission, evidence of benefit is greater for subjects more severely affected by the genetic condition, such as the Hurler or Hurler-Scheie categories of the disease, as well as for subjects with Scheie category more severely affected. Clinical trials or registry information on the safety and efficacy of laronidase in milder cases, such as those patients with less severe symptoms of Scheie Syndrome, would be important in providing adequate information to the MPS I community.